

**AN AETIOLOGICAL STUDY
OF
MILD MENTAL HANDICAP
IN
SOUTHAMPTON SCHOOLCHILDREN**

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Non omnia possumus omnes

- Virgil

The aims of the study were:-

1. - to determine the contribution of recognised medical factors, especially those of genetic origin, to mild mental retardation in Southampton schoolchildren.
2. - to estimate to what extent mild mental retardation in the local population might be preventable by early diagnosis followed by treatment, genetic counselling or prenatal diagnosis as appropriate.

ABSTRACT OF THESIS

This thesis represents the results of a study undertaken to assess the contribution of medical factors, especially those of genetic origin, to mild retardation. Such knowledge would permit appraisal of the potential role of genetic counselling in reducing the prevalence of mild retardation.

Medical histories of 169 Southampton schoolchildren attending schools for the mildly mentally retarded were studied. Each child had a clinical examination, and chromosomal and biochemical analysis. Consideration was given to both those medical features commonly thought to be significant, and to those whose relevance is less certain. Non-medical factors such as parental education and social background were also taken into account.

Medical factors of recognised significance were present in 71 children (42%). These were prenatal in 22, perinatal in 41, and postnatal in eight. Factors of possible, but less certain significance were found in a further 63 children (37%).

In 86 families (51%) there was a history of serious learning difficulties in both parents. The prevalence of both types of medical factors was higher in children whose parents had no educational problems. There were, however, 25 children (15%) whose parents had had no learning difficulties, and in whom medical factors were absent or minimal.

Genetic abnormalities were present in 19 children (11.2%), but were largely sporadic. Hence the scope for reduction in the prevalence of mild mental retardation by genetic counselling would appear to be very limited.

Declaration

I declare that the text of this thesis submitted to the University of Edinburgh for the degree of Doctor of Medicine has been composed entirely by myself, and is based on work done personally under the guidance of Dr N R Dennis, Senior Lecturer in Clinical Genetics at the University of Southampton.

Margaret A. Lamont

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List of Abbreviations

CAH	Congenital adrenal hyperplasia
Cm	Centimetre
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal Fluid
CT	Computerised tomogram
DF	Degree of freedom
DSM III	Diagnostic and statistical Manual of the American Psychiatric Association, 3rd edition
EEG	Electroencephalogram
ESN	Educationally subnormal
ESN/M	Educationally subnormal, mild
ESN/S	Educationally subnormal, severe
FAS	Fetal alcohol syndrome
G-banded	Giemsa banded
GP	General practitioner
HGV	Heavy goods vehicle
Ht	Height
ICD	Inner canthal distance
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IQ	Intelligence quotient
IUGR	Intrauterine growth retardation
IU/l	International units per litre
IVP	Intravenous pyelogram
ml	Millilitres
MMR	Mild mental retardation
MP	Merrill Palmer Intelligence Scale
NHS	National health service
No	Number
OCD	Outer canthal distance
OFC	Occipito-frontal circumference

p	Probability
PKU	Phenylketonuria
SB	Stanford Binet Intelligence Scale
SCBU	Special care baby unit
SD	Standard deviation
SGA	Small-for-gestational-age
VSD	Ventricular-septal defect
WHO	World Health Organisation
WISC	Wechsler Intelligence Scale for Children
χ^2	Chi-squared

Amino Acids

ala	Alamine
cys	Cystine
gla	Glutamic acid
glm	Glutamine
gly	Glycine
hist	Histidine
lys	Lysine
ovr	Ornithine
phe	Phenylalanine
ser	Serine
thr	Thrionine
tyr	Tyrosine
val	Valine

SECTION I - BACKGROUND TO THE STUDY.

1. *The contribution of medical factors to mild mental retardation.*

Medical factors are not generally considered to be a major factor in the aetiology of mild mental retardation (MMR). Many children with MMR have no gross physical defects, nor any outward signs suggestive of underlying cerebral pathology. Their retardation is thought to stem from socio-cultural influences. Indeed, children brought up in families where there is little, if any, interest in their intellectual development will receive little stimulation and have diminished opportunity for learning. Such adverse environmental circumstances, possibly compounding low initial intellectual potential, have been accepted as having a predominant role in MMR, with medical factors contributing little.

Penrose summarised this view in 1938, in his classical report to the Medical Research Council of 1,280 retarded individuals in an institution at Colchester -

"Hereditary and endogenous causes were associated with mild mental defects and affected individuals had few, if any, abnormal clinical features apart from behaviour disorders."

By contrast, severe mental retardation (SMR) is usually associated with physical evidence of impairment of brain function such as spasticity or ataxia and medical causes are identified in the majority of patients.

In the fifty years since the study by Penrose, many medical conditions associated with mental retardation have been identified. Attention has focussed largely on their role in relation to severe retardation, possibly because SMR is usually evident at an early stage in life, and subject to paediatric investigation. MMR often is not recognised

until the child has attended school for one or two years. At this stage retardation is regarded as an educational rather than a medical problem, and medical investigations for aetiology will be few, if any.

However, expanding medical knowledge has led to an increasing number of medical conditions associated with MMR being described. For example, improved cytogenetic techniques have led to the identification of chromosome abnormalities which ten years ago would not have been recognised, and which may be linked with MMR. Additionally, detailed spectrometric analysis of amino acids may detect inborn errors of metabolism, in some of which ensuing mental retardation may be mild. Also, 'new' genetic syndromes featuring MMR are reported frequently in the medical press.

In the light of such knowledge, the traditional view of the aetiology of MMR has been challenged by recent studies (*Hagberg, 1981: Blomquist, 1981: Costeff, 1983: Einfeld, 1984*).

It was felt, therefore, that an investigation of children with MMR, applying current knowledge, would be of value in appraising the contribution of medical factors, especially those of genetic origin, to MMR.

2. *The purpose of the study.*

The study was carried out to ascertain the cause of MMR in affected children, utilising current knowledge of

- genetic syndromes
- chromosome abnormalities
- biochemical disorders.

It was anticipated that a detailed investigation would lead in some children with MMR to an aetiological diagnosis where previously there had been none.

The possible benefits of such a study.

a. Reduction in the prevalence of MMR.

MMR affects up to 2% of schoolchildren (Penrose, 1963) and imposes a heavy burden on educational authorities to provide extra resources. It also, in many cases, involves considerable parental anxiety and family stress.

When a precise diagnosis is known, any genetic implications will become apparent. Where appropriate, families could be offered genetic counselling which would include an appraisal of recurrence risks, consideration of prenatal diagnosis (if available) and the possibility of early diagnosis and treatment of individuals known to be at risk. Knowledge of the genetic contribution would provide a basis for assessing the extent to which MMR in the local community could potentially be reduced.

This assessment was the main aim in investigating children with MMR. It was recognised, however, that a diagnosis could have other benefits.

b. Assessment of prognosis.

A precise diagnosis may be of value in the management of a child with MMR. Complications specific to a disorder could be anticipated and treated early - for instance, the speech disorders and spatial disorientation of Klinefelter syndrome.

c. Support to parents.

A firm diagnosis may relieve parents of anxiety, help them to come to terms with the child's retardation, and to provide realistic support.

d. Guidelines for school medical officers.

In preliminary discussions of the study, it became apparent that school medical officers would welcome guidance about the investigation of children with MMR. Such children in Southampton have a routine school medical examination once a year. This examination is geared towards assessing the child's physical fitness for education and is not normally undertaken with a view to aetiology.

It was hoped, therefore, that results from the study would provide guidelines for investigations likely to be of value for the management of children with MMR.

e. The contribution of environmental factors.

Although the study was directed primarily towards a search for genetic aetiology, environmental medical factors such as birth injury could not be disregarded, and were also studied.

Non-medical factors of familial and social background were also taken into account. Before the study was begun, it was recognised that although environmental factors are difficult to quantify, they may contribute to a large proportion of MMR. In addition, non-medical factors could augment a relatively minor medical insult and result in mental retardation. The study has not, therefore, been confined to a search for genetic aetiology, but has included consideration of environmental factors, both medical and non-medical.

3. *Previous studies in the aetiology of mild mental retardation.*

a. Grade of retardation

"Mildly retarded persons are usually normal in growth and head circumference as well as in most other respects, while those with severe retardation collectively manifest an extraordinarily complex range of handicaps, diseases and syndromes." (*Opitz, 1979.*)

This view that an identifiable cause is present in the majority of patients with SMR, but in a minority of cases with MMR, has been accepted for many years. In studies carried out so far, a medical cause has been identified in the majority of patients with SMR, but less frequently of those with MMR. For instance, in 1963, *Kushlick* in a study of individuals aged 15-19 years in Wessex and Wiltshire, identified an aetiological factor in 70% of 608 with SMR, but in only 38% of 529 individuals with MMR. More recently, *Blomquist (1981)* looking at Swedish schoolchildren, found recognisable aetiology twice as often in children with SMR as compared with those with MMR (43% and 22% respectively).

Thus, studies confined to the aetiology of SMR, and those which do not differentiate between severe and mild retardation in presenting results were not considered appropriate for comparison, and have not been considered.

b. Older studies.

The aetiological spectrum of MMR has changed over recent years. Much of the pathology cited in former studies is now rare in developed countries and direct comparison of older studies is therefore of limited value. *Craib*, in a 1959 study of 44 educationally subnormal children, found, in 8 children, medical pathology which one would not expect to feature now - a history of maternal rubella, tuberculous meningitis, or rhesus incompatibility.

TABLE I.1

MEDICAL AETIOLOGY IN MILD MENTAL RETARDATION - SURVEYS PRIOR TO 1980

Author	Penrose	Kushlick	Craib	Drillien	Innes
Year	1936	1963	1959	1966	1968
Place	Colchester	Wessex/ Wiltshire	London	Edinburgh	N E Scotland
Age Group	All	15-19 years	-	7-14 years	All
Intelligence	Feeble-minded/ borderline intelligence	IQ 50-70	IQ 49-104	IQ 50-69	Feeble-minded
Number studied	627	539	44	209	1565
Medical features (%)	32	38	36	33	16
No Medical features (%)	68	62	64	67	84

Nevertheless, even with the inclusion of such factors, studies prior to 1970 did uphold the impression that MMR is due largely to non-specific socio-cultural factors.

Table I.1 summarises the findings in surveys, carried out prior to 1970, of the aetiology of MMR. These studies were all carried out by checking the records of retarded individuals: they did not attempt further investigation.

The first four studies (*Penrose, 1938; Kushlick, 1963; Craib, 1959; Drillien, 1966*) found identified medical aetiology in approximately one third of cases. In *Innes' (1968)* study under a sixth of feeble minded persons had an evident medical cause.

c. Recent studies.

In spite of advances in knowledge comparable reports since 1980 (Table I.2) have still failed to establish any medical aetiology in over half of mild mental retardates. *Czeizel (1980)* studied 1,364 mentally retarded children aged 8-14 years in Budapest: this included 1,060 children attending special schools for the mildly retarded. Methods used were broadly similar to those of the present study. Biochemical investigation was done on all children, but chromosome analysis was confined to 246 children with physical features suggestive of autosomal or sex chromosome abnormality. No medical factor was identified in 68.5% of the MMR children.

Another comparable survey by *Hagberg (1981)* of children with MMR in Gothenburg included 91 children with IQs of 50-70 and 35 with IQs of 71-75. Nineteen of the former and 17 of the latter were attending normal schools. Children in this study were seen by a paediatrician, but no mention is made of biochemical or chromosome analysis during the survey. 57% had no medical aetiological feature.

TABLE I. 2

MEDICAL AETIOLOGY IN MILD MENTAL RETARDATION - SURVEYS SINCE 1980

Author	Czeizel	Hagberg	Blomquist	Einfeld
Year	1980	1981	1981	1984
Place	Budapest	Gothenburg	N Sweden	Sydney
Age Group (yrs)	7-14	8-12	5-19	0-20
IQ range	50-70	50-70	50-70	52-85
Number studied	1060	91	171	980
Medical cause (%) Total	31.5	43	41	42
Genetic	8.4	5	26	?
Non-genetic	32.1	28	26	?
No Medical cause (%)	68.5	57	59	58

Blomquist (1981) also looked at Swedish children with MMR, but in North Sweden - a predominantly rural area. The 171 children in this study were seen by a paediatrician, but again no mention is made of routine biochemical or chromosome analysis during the survey.

This survey reports a 'medical' finding in 53% of children but this includes children whose MMR was thought to be polygenic in origin - i.e. those who had a parent with MMR but no other 'medical' feature. If this group is excluded - as in the surveys by Czeizel and Hagberg, the percentage of children with recognised medical features in Blomquist's survey is 41%, as shown in Table I.2.

The aetiological grouping in these reports is similar to that used in the present study. Detailed results are compared with those of the present study in the appropriate sections.

In a clinical assessment of 4,500 persons with developmental delay in New South Wales, *Einfeld (1984)* checked computer records. There were no medical aetiological features in 156 out of 249 patients (63%) with borderline - IQ 70-85 - intelligence, nor in 386 out of 731 (53%) patients with MMR (IQ 50-69). Einfeld's study included a wider range of medical features, e.g. prematurity, as being of aetiological significance than in the present study; had such features not been included the percentage of children with no medical aetiological features would have been higher.

4. *The Fragile-X Syndrome.*

None of the studies mentioned so far included a search for the *fragile-X syndrome* which is now known to be an important contributor to mental retardation, especially in retarded males in whom its presence is second only to that of *Down syndrome*.

a. Recognition of fragile-X syndrome.

Lubs first reported an association between mental retardation and a fragile site near the distal end of the long arm of the X chromosome in 1969. The significance of this finding was not fully appreciated until ten years later when *Sutherland* (1979), investigating fragile sites on human chromosomes and relating them to phenotypic effects, concluded that -

"No clinical cytogenetic report on a retarded male can be regarded as complete without positive exclusion of a fragile site (on the X chromosome)."

Subsequent surveys confirmed the association between the fragile-X marker and mental retardation - it was shown to have a prevalence of up to 10% in retarded males (*Blomquist, 1982; Kahkonen, 1983.*).

The range of retardation in the fragile-X syndrome is wide - some males are severely retarded, with little speech, others have MMR. *Gustavson (1981)*, identified 53 affected males. Fourteen had SMR, 39 had MMR. *Blomquist (1983)*, looking specifically for the fragile-X syndrome in children with MMR in Sweden, found 5 out of 110 boys to be affected. *Kahkonen (1983)* also in Sweden, found the fragile-X syndrome in 4 out of 33 boys with MMR.

Female heterozygous carriers may also be affected. *Turner (1980)* studied 128 girls with MMR in an Australian study; of 72 with no physical abnormality, 5 (7%) had the marker X chromosome.

When the present study was being considered, this association between the fragile-X syndrome and mental retardation in males and to a lesser extent in females, was widely recognised.

Assessment of the prevalence of the fragile-X syndrome in local children with MMR was one of the main reasons leading to the study being carried out and it was designed to incorporate a search for this marker chromosome.

b. Genetics

The condition is X-linked; hence there will often be a history of more than one retarded male in affected families.

It is unusual, amongst X-linked disorders however, in that heterozygous female carriers may be affected, with borderline intelligence or MMR (*Herbst, 1980*).

c. Phenotype.

Physical features of the fragile-X syndrome - mild macrocephaly, long face with a high, prominent forehead and prognathism, and large ears - are not especially distinctive and could easily be overlooked. Female carriers may show none of these subtle clinical features (*Turner, 1980*).

Large testes, a feature in post-pubertal males, occur in less than 20% of affected boys.

The features of the fragile-X syndrome were borne in mind when study children were examined.

d. Cytogenetics.

The fragile-X syndrome is detected in only a small proportion of cells examined - usually <30%, with many cases showing levels of 3-4% positive cells. Levels of 2% or under are not usually regarded as significant. (*De Arce, 1983*). Cytogenetic expression of the fragile site requires special culture techniques. The tissue culture medium has to be lower in folate than normal, or have fluodeoxyuridine added (*Hecht, 1982*). Culture time may be extended to 96 hours, as opposed to the more usual 24 or 48 hours, and the amount of colchemid added to arrest mitosis is reduced.

Not all males with mental retardation and physical features of the fragile-X syndrome show the fragile-X even when these special cytogenetic techniques are used. *Fishbaum(1983)* found the fragile-X in 12 out of 18 families with X-linked retardation where the affected males had macro-orchidism; it could not be demonstrated in the other six families.

5. *Biochemical Disorders*

Specific inborn errors of metabolism were first discovered early this century, but it was the description of phenylketonuria (PKU) by *Folling (1934)* that established a link between biochemical disorders and mental retardation. Work done since, especially in the last 20 years or so, has uncovered a vast range of biochemical disorders, many very rare.

Several surveys designed to screen for inborn errors of metabolism, in individuals in institutions for the mentally retarded, have resulted

in previously undiagnosed cases coming to light. *Hill (1972)* found 4 new cases of PKU in 1700 such individuals. Locally, a survey carried out by *Walker et al (1983)* at Tatchbury Mount near Southampton revealed 16 amino acid abnormalities when testing 348 adult patients who had no other evident cause for their retardation. Retarded adults in institutional care tend, however, to have severe mental retardation. Although such surveys may include individuals with MMR, they do not indicate any 'pick up' rate to be expected with MMR.

Screening of study children

The effect of an inborn error of metabolism on brain function varies widely, depending on the toxicity of abnormal metabolites, and the rate of their accumulation in the brain. Some inborn metabolic errors - e.g. oxy-prolinuria - are associated with MMR : in others e.g. histidinuria, cystathionuria - intelligence may be normal or mildly reduced. Aetiological screening of the study children therefore included a search for amino acidurias.

Some of the amino-acidopathies are associated with recognised clinical features, but these may not always be evident in affected individuals. *Hagberg (1969)* reported 2 siblings with homocystinuria. The elder, aged 6 years, was moderately retarded, had the typical sparse hair and eye problems. The younger child, aged 2 years, was clinically normal and retardation was, if present at all, mild.

Urinary screening for abnormal metabolites was, as with cytogenetic analysis, carried out in all survey children, irrespective of any other clinical features.

Neonatal screening for congenital hypothyroidism was introduced in Quebec in 1974, but was not routinely started in the United Kingdom until some years later *Hulse et al, (1980)*. Study children were born prior to this in the early 1970's. Their investigation also included

estimation of blood levels of thyroid stimulating hormone and phenylalanine.

Screening of mothers of study children

Without rigid control of diet, mental retardation occurs in about 90% children born to mothers with PKU (*Lemke, 1980*). A benign form of PKU may, however, occur unsuspected in adults functioning normally in society. Mental retardation can occur in children born to mothers with undiagnosed PKU - although such children do not have PKU themselves (*Mabry, 1966; Hill, 1972; Perry, 1973*). This maternal-child link has not been evident in other amino-acidopathies, but it was felt that this study would provide a useful opportunity to extend the PKU check to include a search for other possible undiagnosed amino-acid-patterns in the mothers of retarded children. For this, mothers had a urine check for abnormal metabolites, and also quantitative amino-acid analysis in serum.

Summary - Section I

Prior to the present study, surveys designed to look for possible genetic aetiology in children with MMR had not included routine chromosome analysis, including a search for the fragile-X chromosome, as well as a clinical and biochemical assessment.

It was felt that the present study in which each child had a detailed examination - looking particularly for genetic syndromes - biochemical investigation and chromosome analysis - including a fragile-X check - would combine all the diagnostic techniques presently available, and provide an up-to-date assessment of medical aetiology in MMR.

SECTION II. MILD MENTAL RETARDATION

The terms - mental deficiency
 mental handicap
 mental retardation
 - are all in international use.

In this study the term "mental retardation", used by the World Health Organisation (WHO) is used throughout.

1. *Definition*

Intelligence Tests

Age standardised tests are widely used to measure intelligence, and when applied to the general population, provide a "norm" of intelligence and standard deviations (*SD*).

The intelligence quotient (*IQ*) is calculated from the degree of deviation from the average score for the relevant chronological age (*Thorndike, 1925*).

The mean is 100 points with an *SD* of 15 points.

Measurements of intelligence obtained by standardised tests provide relative, not absolute, values. Although the tests used are designed to minimise the influence of socio-cultural factors, they are not entirely independent of such factors.

IQ levels provide a guide to the level of intelligence, but are not a specific measure.

There is a gradual upward trend in intelligence. The tests used are standardised every ten years to maintain a norm of 100. Over 42

years, white Americans have had a gain of a full SD in IQ scoring. (Flynn, 1982.)

The IQ score gained by an individual may fluctuate. A stimulating environment and educational demands may raise the score.

However, within these various limitations, the empiric values given by present tests do provide a useful guide to levels of intelligence.

The WHO report of 1968 defined mental retardation as existing when the IQ was equal to or greater than 2 SD below the mean, and put the upper limit of mild mental retardation at IQ 70 (or 75), the lower at IQ 50. (Table II.1).

Hence - mild mental retardation IQ 50-70 [75]

In practice, mentally retarded individuals are usually divided into two groups.

Those with IQs <50 have severe mental retardation.

Those with IQs 50-70 have mild mental retardation.

Recently, consideration has been given to social adaptation as well as intelligence tests.

TABLE II.1

Classification and distribution of mental retardation proposed by
WHO Expert Committee on Mental Health in 1969

Groups	IQ	Proportion of all mentally retarded (%)
Profound	0-20	5
Severe	20-35	20
Moderate	35-50	-
Mild	50-75 (or 75)	75

Reproduced from WHO Technical Report Series, NO. 392, 1968.

The WHO report on mental retardation of 1985 states -

"The assessment of intellectual level should be based on whatever information is available, using clinical evidence, adaptive behaviour and psychometric findings".

The recognition that social, as well as intellectual, skills have to be considered has meant that the boundaries of MMR have become blurred, especially in the upper IQ ranges.

Educationalists now recognise a category of "borderline intelligence" - with IQ 70-85: other workers accept an IQ of 75 as the upper range of MMR.

2. *Prevalence of mild mental retardation.*

As already discussed, although the lower limit of mild mental retardation is generally regarded as IQ 50, definition in the upper IQ ranges is not clear cut. An individual with an IQ just <70, but with good social adaptation, may not necessarily be classed as having MMR. Conversely, those with IQs slightly >70 but with poor social adaptation, may come into the MMR range. This blurring of the upper borders causes problems in determining the prevalence of MMR.

Intelligence in the general population follows a continuous Gaussian distribution (*Thorndike, 1925*). One would expect, with a mean of 100 and an SD of 15, just under 2% to come within the range 50-70 (-3.3 to -2 SD). Various authors have found the prevalence of MMR in the total school population, in children aged 7-14 years, to be < 1% (Table II.2), but in none of these surveys did all children have formal IQ testing. Where social adaptation is adequate, a mild reduction in IQ may go unrecognised. *Birch (1970)* out of a total of 8,274 Aberdeen schoolchildren aged 8-10 years, found 123 (1.4%) to be functioning normally, but with IQs <75: a further 104 (1.26%) had been identified as having mild mental retardation. Less than half of those Aberdeen children with IQs <75 had been officially classed as being mildly retarded. *Hagberg (1981)* from a total of 24,498 children aged 8-12 years in Gothenburg, identified 90 children with IQs 50-75 in special schools - a prevalence of 0.37%. Another 36 were attending normal schools - a total prevalence of 0.5%.

Even if one regards children with IQs below 75, who are functioning normally in mainstream education, as having MMR, the prevalence of MMR has varied from - 0.3% to 3.2% - in different surveys, a range which reflects the problems of both definition and ascertainment.

TABLE II.2

PREVALENCE OF MILD MENTAL RETARDATION IN PREVIOUS STUDIES

Author	Year	Place	Total cohort	Age Range (years)	Grading	Prevalence of MMR (%)
Drillien	1965	Edinburgh	39,498	7-14	IQ 50-69	0.53
Innes	1968	N E Scotland	1,565	unlimited	'feeble-minded'	3.26
Birch	1970	Aberdeen	8,274	8-10	IQ 50-75	2.75
Hagberg	1978	Gothenburg	24,498	8-12	IQ 50-70	0.37
Czeizel	1980	Budapest	?	7-14	'MMR'	3.00
Blomquist	1981	N Sweden	40,871	8-19	IQ 50-69	0.42

3. *ESN/M schools*

a. Educational role.

The *Education Act of 1971* states that-

"a child has special educational needs if he has a learning difficulty which calls for special educational provisions for him."

This special educational provision is supplied in educationally subnormal (*ESN*) schools; *ESN/M* for children with mild mental retardation, *ESN/S* schools for children who are severely retarded. Staff at *ESN* schools are specially trained and skilled in teaching children with educational problems; there is a lower pupil:teacher ratio than in normal schools.

b. Referral to *ESN/M* school.

The majority of children in *ESN/M* schools have been in mainstream education for two or three years prior to referral. Their inability to keep up with classmates may become apparent only as educational demands increase. The regular teacher may initially give the child extra help and part-time remedial teachers may be used; acceptance that the child is not progressing satisfactorily will be gradual. The peak age of referral is 7-8 years.

Children being considered for referral to an *ESN/M* school are usually seen by an Educational Psychologist, although not all have formal IQ tests at this stage.

Several factors may influence referral of a child with learning problems -

- parental opinion
- school status
- availability of places
- previous history
- behaviour problems

Parental opinion.

Parents are consulted: a child may not be referred to an ESN/M school without their consent. Parents may refuse permission if they think that the 'stigma' of attending an ESN/M school is likely to outweigh possible benefit from specialist teaching.

School status.

Referrals may, to some extent, depend on the status of the mainstream school. A child with learning problems may be referred more readily where the general standard of ability is high. Referral may be postponed, or bypassed if classes are small, and the teacher can perhaps devote more time to a backward pupil. Conversely, where classes are small, children with learning problems may be more readily identified, and in small village schools opportunities for remedial education may be reduced.

Availability of places.

The three ESN/M schools in Southampton provide sufficient places for any children who would be expected to benefit from special education. In this region, lack of adequate provision is not a factor limiting referral.

Previous history.

Recognition of MMR prior to school entry is exceptional, and is usually associated with evident physical or neurological defects.

Such children are likely to be under medical supervision, and the risk of being educationally subnormal is known.

There is in Southampton an assessment centre for pre-school children with evident development problems. A few children are referred from this unit directly for ESN/M education at the age of 5 years.

Behaviour problems.

A child of borderline or subnormal intelligence may be more readily referred if behaviour problems cause disruption in the class in normal school.

This aspect was studied in the survey, and did not appear to have influenced referral. (*Section III B.5*)

Summary - Section II

MMR has a lower IQ limit of 50. The upper limit is officially 70; IQ 75 is also accepted. However, in practice there is no fixed upper IQ score, with social adaptation influencing the diagnosis of MMR. The true prevalence of MMR cannot therefore be measured precisely.

ESN/M schools provide education for mildly educationally subnormal children: referral to such schools is not automatic for all children with learning difficulties.

SECTION III - STUDY POPULATION

The study population comprised 169 children - 97 boys, 72 girls.

1. Recruitment

1. Age cohort.

It was drawn from children aged 7-11 years, who at the time of the study were attending one of the three schools which provide ESN/M education for pupils up to the age of 11 years in the Southampton area.

The study took place in 1982-1984 and children included were born between 17 August 1971 and 31 July 1976.

2. Schools in the survey.

The three schools involved were;

- Forest Edge School, which draws children from the western boundaries of Southampton City, from a large housing estate associated with an oil refinery outside the city, and from rural areas in the New Forest.

- Vermont School, which covers the urban central and northern areas of Southampton City.

- Netley Court School, which covers the eastern part of the city, where there are several large private housing developments, as well as older housing estates.

Although, for reasons already discussed, there may well be children with MMR in mainstream education, it was decided at an early stage not to include such children in the study. Ascertainment of children with

MMR in normal schools would be difficult, as formal IQ testing is not done routinely in Southampton schools. Furthermore, inclusion in the study of children with learning problems, but whose parents did not accept that they had MMR, might have caused resentment.

3. Procedure for recruitment into the study.

The study was commenced following approval of the study by the local Ethical Committee.

a.

A meeting was held with the headteacher and staff of each of the three schools in turn, to explain the purpose and nature of the project, and to ask for their cooperation. This was willingly given by all involved. Each school provided a list of pupils attending along with their dates of birth and home addresses.

b.

For children born within the selected five year period, school medical records were consulted for the names of family doctors, and to check that children were living with one or both parents. Because family studies formed part of the investigation, 6 children who were fostered - none were adopted - were not included.

c.

A letter, (*Appendix A*) with a brief explanation of the project was sent to the family doctor of each child. This afforded an opportunity to reply if it was felt that it would be inappropriate to approach any family about the study.

One doctor kindly wrote back mentioning social problems in a family, but none suggested that it would be inadvisable to approach any family.

d.

Letters (*Appendix A*) outlining the purpose and nature of the study, along with a note of approval from the relevant headteacher, were sent to the parents of eligible children. The letter also suggested a time for a home visit to discuss the study in more detail.

A stamped addressed envelope was enclosed, with a reply slip which gave parents the option of refusing to take part in the study or of suggesting an alternative time for the home visit if the time suggested was inconvenient.

e.

If no reply was received, parents were visited at home at the pre-arranged time.

If, after discussion, parents agreed to participate, their signed permission was obtained to examine the children at school, and to take blood and urine samples.

f.

In those families where parents did not reply to the letter, but were not at home at the time arranged for the visit, a second letter, with an alternative time, was sent.

If again, there was no response to the letter, and the second home visit was unsuccessful, the child was not included in the study.

From a total of 231 eligible children, parents of 177 agreed to take part in the study. Table III.1 gives details for the three schools involved.

4. Children not included.

Twenty-three parents declined to take part by letter. One father wrote to say that he felt his child had already been adequately investigated: no reason was given by 22 parents.

Thirteen parents declined to participate after discussion at the home visits. For the study, a blood sample was required from the mother, and also the child. An aversion to venepuncture was the usual reason for non-participation.

Three families who agreed to take part moved out of the area prior to the home visit. Another 3 were seen at home but moved soon after, before the child was seen at school.

Two children were transferred from ESN/M education after the home visits. One, a girl with Down syndrome, returned to mainstream education and one girl with William syndrome went to an ESN/S school.

TABLE III.1

Reasons for non-inclusion in the survey of 62 eligible children attending ESN/M schools in Southampton.

SCHOOL	Forest Edge	Vermont	Netley Court	TOTAL
No. of eligible children	77	80	74	231
Parents refused to cooperate -				
by letter	9	8	6	23
at home visits	5	4	4	13
No reply at home visits on two successive occasions	3	7	8	18
Child left prior to school visit	3	3	2	8
No. not included	20	22	20	62
No. included	57	58	54	169

Two children who were transferred to ESN/M education during the course of the survey were not included as their parents did not wish to take part in the study.

B.

Intelligence tests.

One hundred and sixty-four children had had formal intelligence tests.

Five children not tested had severe behaviour problems and IQ assessment had not been attempted.

1. Tests used.

Intelligence was rated using:-

Wechsler Intelligence Scale for Children (WISC) (1958).

Stanford-Binet Intelligence Scale (SB) (1960) - as revised by Terman (1960).

Merrill Palmer tests (MP) - as revised by Stephen (1975).

Over half the children had been tested using the WISC method; their mean IQ was 67.5. Children tested by the SB method had a mean of IQ 68.6. Children tested by the MP method had a mean of IQ 67.7.

Table III.2 shows the number of children tested by each method, in the three schools, with mean IQ results.

Because of their emphasis on educational and verbal items, tests using the Stanford-Binet and Merrill Palmer methods of intelligence assessment have been criticised as discriminating against children with a disadvantaged background. I therefore looked at results using the Wechsler and Stanford-Binet/Merrill Palmer scales in children from Social Class V. (Table III.3)

TABLE III.2

IQ rating by tests used and school.

SCHOOLS	Forest Edge		Vermont		Netley Court		Total	
TESTS	No.	Mean IQ	No.	Mean IQ	No.	Mean IQ	No.	Mean IQ
Wechsler	35	70.3	24	66.3	28	65.5	87	67.5
Stanford-Binet	17	70.2	31	66.5	18	69.1	66	68.6
Merrill-Palmer	-	-	3	65.0	8	68.8	11	67.7
Not tested	5	-	-	-	-	-	5	-
TOTAL	57	70.3	58	66.4	54	67.2	169	67.9

TABLE III.3

IQ rating in 50 children from Social Class V by test used

TEST	NUMBER TESTED	MEAN IQ
Wechsler	27	68.6
Stanford-Binet/ Merrill Palmer	23	68.3

$$t=0.13, DF=48 : p \gg 0.5$$

There were 52 study children from Social Class V. Two had not had formal testing. In the social class V children tested, the difference in mean IQ rating according to the test used was not statistically significant. In overall consideration of IQ rating in the children, I have not therefore distinguished between tests used.

2. Mean IQ

Mean IQ in the study population was 67.8, with an SD of 6.6.

3. IQ Rating by school

Five children - all attending Forest Edge School - had not been tested. Details of IQ rating in 164 children tested at the three schools are shown in Table III.4.

TABLE III.4

IQ mean, standard deviation, and mean age in 3 ESN/M schools

SCHOOL	No. of children	Mean IQ	(S.D.)	Mean age (years)
Forest Edge	52	70.3	(6.7)	8.7
Vermont	58	66.6	(6.8)	8.9
Netley Court	54	67.2	(6.4)	8.9

The mean IQ of children at Forest Edge School is seen to be 3-4 points higher than in the other two schools.

Because children in the lower IQ ranges might be referred to ESN/M schools at an earlier age, a higher mean age at Forest Edge might

account for this IQ difference. However, children at Forest Edge School were slightly younger, on average, than children in the other two schools: the age of referral was not a relevant factor.

The catchment area of Forest Edge School differs from the other two schools in that it includes, as well as a large council housing estate, rural areas of the New Forest, with small village schools.

Children in the other two ESN/M schools are drawn mainly from the City of Southampton. A possible shift in the pattern of referral from small village schools to ESN/M schools has already been discussed. In the smaller classes of village schools, borderline intelligence may be more easily recognised, and facilities for remedial education within mainstream education less readily available. Grouping children into those with IQs equal to or less than 70, and those with IQs >70 - (Table III.5) - it was seen that 60% of children at Forest Edge School had IQs >70, compared with 34% at Vermont and 44% at Netley Court. This difference however, was not significant ($0.5 > p > 0.10$) and therefore in presenting results, I have not considered the three schools separately.

It was somewhat surprising to find that, overall,

46% of study children had IQs >70.

TABLE III.5

Number of children of IQ rating equal to or less than 70 and >70
in three ESN/M schools.

SCHOOL	Forest Edge	Vermont	Netley Court	Total
IQ equal to or less than 70				
No. (%)	21(40)	38(66)	31(57)	90(55)
IQ >70				
No. (%)	31(60)	20(34)	23(43)	74(45)
Total	52	58	54	164

[DF = 4: $\chi^2 = 6.6$: 0.5> $p>0.10$]

4. IQ rating in the study population by sex (Table III.6)

In children with IQs equal to or more than 60, and in the 60-70 IQ range, boys and girls were represented equally (48%, 52% respectively) but there was a significant difference ($p>0.01$) between this sex distribution and that of children with IQs >70. In this latter group there were twice as many boys as girls.

TABLE III.6

IQ distribution by sex in 164 ESN/M children

IQ Range	Males	Females	Total
48-60	15	15	
61-70	29 } 44	31 } 46	90
71-80	39	23	
81-85	10 } 49	2 } 25	74
Total	93	71	164

$$[x^2 = 5.5 : DF = 1 : 0.02 > p > 0.01]$$

TABLE III.7

Prevalence of behaviour disorders in 93 male and 71 female ESN/M children with IQ equal to or less than 70 or >70

Behaviour disorder	Male		Female	
	IQ equal to or less than 70	IQ >70	IQ equal to or less than 70	IQ >70
disorder	5	4	7	3
Total	43	50	46	25

$$[\text{Male} - x^2 = 2.15 : DF = 1 : 0.50 > p > 0.10]$$

$$[\text{Female} - x^2 = 0.02 : DF = 1 : p > 0.5]$$

5. Possible influence of behaviour disorders on referral

The possibility that children, especially boys, might be referred more readily for special education if they had disruptive behaviour, was considered. Behaviour problems, however, showed little sex differential.

Twelve out of 97 (12.3%) boys had behaviour problems, compared with 9 out of 72 (12.5%) girls: (this includes all study children including those with no IQ assessment).

Looking at children who had known IQ ratings, the prevalence of behaviour disorders in those with IQ equal to or less than 70, or >70, did not differ significantly in males or females. (Table III.7).

It therefore did not appear that children, especially boys, of borderline intelligence were more readily referred for special education if they had behaviour problems.

6. Sex differential in study children of borderline intelligence

There is no reason to suppose that the 2:1 male:female ratio in the study children of borderline intelligence (Table III.6) reflects the population prevalence rate.

A possible explanation for the sex differential in study children may be that boys aged 7-11 years may be less socially adept than their female peers, and hence that those of borderline intelligence could be more likely candidates for ESN/M referral. Boys may also have slower maturation than girls. It has been estimated (*Richardson, 1986*) that at 6 years, girls are 12 months ahead of boys, and by 9 years, 18 months ahead in school performance.

7. Ascertainment of children with MMR

As discussed in Section II. 2 above, one would expect 2% of the population to have an IQ rating between 50 and 70 ($- 2$ SD.)

At the time of the study, the total school population in the age range and geographical district covered by the study was 11,291.

Of these 11,291, 237 children attended the three ESN/M schools. This is equivalent to 1.98% of the local school population.

The IQ distribution is known for 164 children in the study. There is no reason to suppose that this IQ distribution differed from that of 62 eligible children not in the study, nor of the 5 study children not tested.

Eighty-nine out of 164 (54%) study children had IQs equal to or less than 70. For the total ESN/M school population, the equivalent number would be 127.

Hence, if 127 out of 11,924 - 1.06% - schoolchildren with IQs equal to or less than 70 attend ESN/M schools, ascertainment of children with IQs 50-70 must be about 50%.

Birch (1970) looking at schoolchildren in Aberdeen, where IQ testing was done routinely, found that 123 out of 227 children with IQs equal to or less than 75 were attending normal schools.

I acknowledge that the present study by no means includes all children with MMR in Southampton; it includes only those referred for special education. As IQ testing in Southampton is carried out only in children being considered for ESN school referral, it was not feasible to identify children in normal schools with IQs equal to or less than 70.

On the basis that children are referred for special education because they cannot cope in normal schools, the study has included children in attendance at ESN/M schools irrespective of IQ rating.



Summary - Section III

1. The study population consisted of 169 children - 97 boys, and 72 girls, aged 7-11 years, receiving ESN/M education in Southampton in 1982-1984.

2. It was drawn from 237 pupils, which represents 1.98% of the total school population of 11,291 in this age group.

3. The IQ range was 48-85; 5 children had not had formal IQ assessment.

4. 46% of study children had IQs >70. There was no sex differential in children with IQs equal to or less than 70; in those with IQs >70, male:female ratio was 2:1.

5. The presence of behaviour disorders did not influence referral.

6. Attendance at ESN/M schools, irrespective of IQ levels, has been used as the criterion for inclusion in the study.

SECTION IV - PROCEDURE OF THE STUDY

Following approval of the study by the local Ethical Committee, children from the three ESN/M schools covering the Southampton area were recruited into the survey as described in Section III - 3, a.

Information for the study was collected as follows -

1. Home visit

Parents who agreed to take part in the survey were interviewed at home before the children were seen at school.

A family history was taken - this included medical and educational histories of all first and second degree relatives of the parents.

Parents were also asked about their own occupations, medical and educational backgrounds, and for details of pregnancies and the births, early development and education of all children.

Details were recorded in a form shown in Appendix B.

A urine sample, and a 10 ml. non heparinised blood sample, for amino-acid analysis, were obtained from the mother of the study child.

Written permission was obtained to take a blood and urine sample from the study child, at school.

[Form - Appendix B]

2. Medical records

Medical information given by parents was supplemented with that in the school medical records, and in any available hospital records.

Details of hospital attendances or admissions and investigations, were recorded alongside those given by the parents. [*Form -Appendix B*]

Obstetric details of children born outside Southampton area were requested from the relevant hospital. [*Form - Appendix B*]

3. School visit

All children were examined personally, and individually, at school.

All school and home visits were completed for one school before visiting the next - in the order

Forest Edge School
Vermont School
Netley Court School

A. Clinical information

Details of the clinical information were recorded in the form shown in Appendix A.

Measurements included:-

height
weight
occipito-frontal circumference (*OFC*)
outer canthal distance (*OCD*)
inner canthal distance (*ICD*)

As well as the routine clinical examination, a careful check was made for any dysmorphic features including:-

- | | |
|----------------|--|
| Skull | - abnormal overall shape |
| | - asymmetry |
| | - frontal bossing |
| Ears | - protruding, + or - large |
| | - posterior rotation |
| | - simple form |
| | - preauricular skin tag/sinus |
| | - incomplete development of upper helices |
| Eyes | - inner epicanthic folds |
| | - mongoloid/anti-mongoloid slant to palpebral fissures |
| | - hypertelorism |
| Face and mouth | - high, narrow palate |
| | - micrognathia, prognathia |
| | - small oral opening |
| | - long/short philtrum |
| | - thick/thin lips |
| | - dental abnormalities |
| Thorax | - widely spaced nipples |
| | - scoliosis, kyphosis |
| | - asymmetry of chest wall |
| | - pectus excavatum/carinatum |
| Abdomen | - umbilical hernia |
| | - diastasis recti |
| Genitalia | - mild hypospadias |
| | - small penis |
| | - small/large testes |
| Hands | - clinodactyly, and other minor malformations of fingers |
| | - simian crease |
| | - dermatoglyphic abnormalities |

- finger webbing
- abnormal finger creases
- nail abnormalities
- Feet - abnormal shape, insertion of toes
- syndactyly of toes 2/3, 3/4
- Skin - abnormal pigmentation
- hirsutism
- deep sacral dimple

Children suspected of having a genetic syndrome, or with three or more dysmorphic features, were seen again at school, for reassessment in conjunction with Dr N Dennis. The presence of three or more dysmorphic features was considered to be significant as discussed in Section VII,2.

Scoring of individual dysmorphic features has not been used in this study - such practice is not in common use amongst dysmorphologists. Assessment of features is largely subjective, and most do not lend themselves to measurement; scoring is empiric. Any assessment - even of the presence or absence of a minor dysmorphic feature - is notoriously difficult - when is a high palate "high"? In order to overcome, to some extent, the subjective element in assessing dysmorphic features, a group of control schoolchildren were also examined by the author (*Section III,6*).

B. Co-ordination testing

Five tests were used to assess co-ordination.

1. Tapping the back of each hand rapidly with the fingers of the other hand.
2. Finger - thumb apposition - in which each finger in turn is apposed to the thumb.

3. First finger - nose apposition, with the eyes closed.
4. Heel - toe walking, along a straight line.
5. Hopping: 5 or 6 hops on each foot.

The child's performance in each test was rated as satisfactory or poor. Poor performance in 2 or more tests was taken to indicate incoordination.

C. Collection of blood and urine samples

A 5 ml. blood sample was taken into a lithium heparin tube, from each child.

A Guthrie blood spot card was also completed for each child.

With the help of the school staff, a urine sample was obtained.

4. Laboratory tests

a. Urine samples

Urine samples from mothers and children were tested personally within 4 hours of collection.

Samples were tested using -

Labstix - to test for

- pH, protein, glucose, ketones, bilinogen and urobilinogen.

Phenystix - to test for

(Ames)

- phenylpyruvate.

Clinitest - to test for

(Ames)

- reducing agents. (*present in diabetes mellitus, galactosaemia fructose intolerance.*)

Dinitrophenylhydrazine test for

- ketones. (*present in phenylketonuria, maple syrup urine disease, histidinuria, tyrosinosis.*)

[250 microlitres of a saturated solution of 2,4 Dinitrophenylhydrazine in 2M HCL is added to 250 microlitres urine. A cloudy deposit indicates ketones.]

Cyanide nitroprusside test for

- Cystine, cysteine and homocystine. (*cystinuria, homocystinuria.*)

[250 microlitres of 5% potassium cyanide in H₂O is added to 500 microlitres urine in a Luckham tube. One drop of a fresh saturated solution of nitroprusside is capped and left to stand for 10 minutes. Magenta coloration is positive.]

b. Blood samples

MATERNAL - Biochemical analysis

As soon as possible after collection, mothers' blood samples were centrifuged at 1000 revolutions per minute for 5 minutes. The serum was separated off and frozen. When a batch of 10-20 samples had been collected, they were run together on a *Rank-Hilger-Chromaspeck* amino acid analyser, by Dr P. Smythe under the direction of Professor B. Clayton, in the department of Chemical Pathology, University of

Southampton. This machine automatically analyses the concentration of amino acids in serum.

Amino acids checked and their normal ranges, are given below.

AMINO ACID	Threonine	Serine	Glutamic Acid	Glutamine	Methionine
(IU/1)	75-250	61-90	0-120	420-760	13-39

AMINO ACID	Isoleucine	Leucine	Tyrosine	Proline	Glycine	Alanine
(IU/1)	35-100	69-160	32-87	89-440	130-490	170-500

AMINO ACID	Cystine	Valine	Histidine	Tryptophan	Ornithine
(IU/1)	31-140	120-330	56-120	10-80	31-130

AMINO ACID	Lysine	Arginine
(IU/1)	90-260	46-150

CHILDREN - Cytogenetic analysis

Children's blood samples and the Guthrie spot cards, were sent by first class post for analysis to Salisbury General Hospital. Chromosome analysis was done in the Salisbury Cytogenetic Laboratory under the direction of Dr Marina Seabright.

Cultures were set up in low-folate Iscove medium to encourage expression of the fragile-X chromosome and harvested at 48 or 72 hours.

Thirty metaphases from G-banded preparations were examined for each child,

A repeat analysis was done on children karyotyped prior to the survey, to screen particularly for the fragile-X syndrome. Where an abnormality was found that could be familial, both parents had their chromosomes analysed.

- Biochemical analysis

The Guthrie blood spot cards were processed by Dr G. Batstone, in the Salisbury Biochemistry laboratory. They were punched out, the samples placed in assay tubes, and screened for phenylalanine and thyroid stimulating hormone, using a double antibody technique.

5. Relaying results

When results were normal, a standard form was sent to general practitioners for inclusion in the child's case record. A letter was sent to those parents who had requested this. (Both the form and the letter are shown in Appendix B).

Where results were abnormal, the general practitioner was informed by letter; abnormal results were not relayed directly to the parents.

6. Examination of control school children

The headteachers of three primary schools in South Hampshire were asked if they would be willing to have children examined at school, to act as controls for dysmorphic features. The Author had access to these schools through community work. All agreed, and written permission was sought from all parents of children in the appropriate age range, to examine their children at school.

The control children were within the same age range as the study children, but attended normal schools. They did not have formal IQ testing and were not individually matched to study children. No

details were known of their medical, educational, or socio-cultural backgrounds.

They were measured and examined in the same way as study children, for measurements, dysmorphic features and incoordination.

Summary - Section IV

1. Ethical approval for the study was followed by visits to the 3 ESN/M schools involved to explain the purpose of the study, seek the approval of the staff and obtain names of pupils attending.

2. Parents of study children were visited at home, where details were obtained of the medical and educational histories of the parents, and first and second degree relatives.

Information about the mothers' pregnancies, and the births and early development of the study children and their siblings was noted.

Blood and urine samples were collected from mothers.

3. At school, study children had a detailed clinical examination, looking especially for dysmorphic features. Coordination was tested. Blood and urine samples were obtained.

4. Hospital medical records, where available, were checked to supplement information provided by mothers and school medical records.

5. All urine samples were checked for abnormal constituents.

6. Maternal blood samples had amino acid analysis, children's blood samples were screened for chromosomal abnormalities, and for hypothyroidism and phenylketonuria.

7. A group of children attending normal schools were examined clinically to act as controls for dysmorphic features.

MEDICAL CONDITIONS PRESENT IN STUDY CHILDREN

Findings in sections V, VI and VII have been published in the *Archives of Disease in Childhood*, 1988: 63: 1032-1038; a reprint of this article by M.A.Lamont and N.R.Dennis is included in *Appendix C*.

Medical features found in the study children have been divided into three main groups.

Section V - known risk factors.

- features whose aetiological role in mental retardation is recognised, and which probably contributed to ESN/M referral.

Section VI - possible risk factors.

- features having no firm association with mental retardation, but of possible aetiological significance.

Features in sections V and VI have been classed as of -

prenatal
perinatal
postnatal
origin.

Section VII - features of uncertain origin.

- Included in this grouping are features whose origin cannot be ascribed to a specific event and which, although unlikely to be of aetiological significance per se, may indicate underlying pathology which could be of aetiological significance in mental retardation.

In presenting results, relevant findings for each child are given in tables, with, where appropriate, further details in the text. There has been some inevitable overlap in presenting details of children who had features in more than one group. In the tables relating to each feature, concomitant medical features of probable aetiological significance are underlined. Home circumstances shown in the tables are discussed in Section VI.

Full details of findings in each child, with photographs, are given in *Appendix B*. Reference is made to these individual case reports by appropriate number in the presentation and consideration of results.

SECTION V- PRENATAL FEATURES OF PROBABLE AETIOLOGICAL SIGNIFICANCE

A. PRENATAL FEATURES

Prenatal features of probable aetiological significance were identified in 22 children;

- of genetic/part genetic origin in 19.
- of environmental origin in 3.

Table V.1 summarises these findings.

TABLE V.1

Prenatal features of probable aetiological significance in
22 out of 169 ESN/M children.

	Number	(%)
Chromosome abnormality	8	(4.8)
Mendelian genetic syndrome	2	(1.2)
Non-Mendelian genetic syndrome	3	(1.8)
Malformation of the central nervous system	5	(3.0)
Inborn error of metabolism	1	(0.6)
Infection	2	(1.2)
Alcohol fetopathy	1	(0.6)
<hr/>		
Total	22	(13)

PRENATAL MEDICAL FEATURES

1. CHROMOSOME ABNORMALITIES

Chromosome abnormalities found in the pupils attending ESN/M schools have been reported separately in

Archives of Disease in Childhood, 1986: 61: 223-226

- M.A.Lamont, N.R.Dennis, M.Seabright.

A reprint of the article is included in *Appendix C*.

Details of the methods of chromosome analysis are given in *Section IV, 4, b*.

Results

a.

Chromosome analysis was performed on 166 children -

96 boys, 70 girls.

In one child venepuncture was unsuccessful on two occasions, and was not tried again.

In eight samples the initial culture failed. No attempt was made to obtain a repeat sample in two children who had been very upset by the original venepuncture.

b.

Nine children had major chromosome abnormalities (Table V.2) but the presence of a familial, apparently balanced, translocation in one child [59] was not regarded as being of aetiological significance.

TABLE V.2

Major chromosome abnormalities, with other features,
in 9 out of 166 children from ESN/M schools.

Case No.	133	111	7	106	40
Karyotype	47,XX+21	47,XX+21	46,XY dup.14 (q21-q22)	47,XXY	47,XXY
IQ	64	74	69	72	76
Maternal age at birth	38	48	20	24	38
Paternal age at birth	43	52	33	20	46
Birth weight (g)	3373	3040	3146	3800	2182
Factors in pregnancy	-	Mild hypertension	-	-	Hypertension. Placental insufficiency.
Perinatal factors	-	-	Jaundice	-	<u>Low Apgar score</u>
Early motor delay	-	-	+	-	-
Early speech delay	+	-	+	+	+
Dysmorphic features	Down syndrome	Down syndrome	Microphthalmos, short digits, Simian crease.	-	-
Home background	Average	Average	Average	Poor	Poor
Other features	-	-	Mother-46,XX Father-46,XY Hirschsprung's disease- 1 year.	-	Mentally retarded brother

TABLE V.2 (continued)

Major chromosome abnormalities, with other features, in 9 out of 166 children from ESN/M schools.				
Case No.	21	35	107	59
Karyotype	48,XXYY	46,Xt(X;19) (p11.2;q13.3)	46,XX del.15 (q11.2;q13.1)*	46,XY,t(3:15) (p11;q12.2)
IQ	68	74	66	48
Maternal age at birth	25	23	39	23
Paternal age at birth	27	29	38	49
Birth weight (g)	3061	2353	2780	2870
Factors in pregnancy	-	Excess alcohol intake.	Hypertension	-
Perinatal factors	-	-	Low Apgar score	-
Early motor delay	+	-	-	+
Early speech delay	+	-	-	+
Dysmorphic features	Mild bilateral clinodactyly. Shield chest.	-	-	High, narrow palate. Tongue tie. Bilateral clinodactyly.
Home background	Average	Poor	Average	Poor
Other features	Behaviour problems.	Mother-46,XX Father-46,XY	Mother-46,XX Father-46,XY	Epilepsy. Behaviour problems. Mother, grandmother - 46,XXt(3:15)

* Fragile X present in 2 out of 225 cells.

c

Six of these chromosome abnormalities were identified in the survey. Ironically, the only child of these 6 to have evident dysmorphic features, was the child [59] with the familial balanced translocation. His mother and maternal grandmother both carried the same translocation, and had normal phenotypes. This is discussed further in Section VII, 2, iv.

d.

With the exception of this balanced translocation, all chromosome abnormalities in the children had occurred de novo.

e.

Maternal age - Mothers of children [40,107,111,133] were aged 38 years or over when the affected child was born.

f.

Fragile-X - No survey children were found to have the fragile-X chromosome. The girl [107] with a deletion of chromosome 15 had one X chromosome with a possible fragile site in 30 cells in the initial culture analysed. A repeat specimen, incubated with uracil and also with uracil and caffeine - a technique thought to enhance expression of the fragile-X site (*Yunis, 1984.*) - showed fragile-X in 2 out of 225 cells examined. This was not regarded as significant. Both her parents had normal karyotypes.

TABLE V.3

Chromosome abnormalities in reported surveys of children with MMR

Author	Year	Place	Cohort	Overall prevalence of chromosome abnormality (%)	Trisomy 21 (%)	Sex chromosome aneuploidy (%)	Other chromosome abnormality (%)
Czeizel	1980	Budapest	1,060	3.2	?	1.2	?
Hagberg	1981	Gothenberg	91	4.0	2.0	1.0	1.0
Blomquist	1981	Sweden	171	8.0	6.4	?	1.6
Einfeld	1984	New South Wales	731	8.4	7.1	0.3	1.0
Present Study	1986	Southampton	169	5.3	1.2	1.8	2.3

COMMENTS

- a. *Prevalence of chromosome abnormalities in MMR, and in this survey.*
 - Summarised in Table V.3.

Although chromosome abnormalities are known to be an important cause of SMR, accounting for over a third of all individuals with IQs <50 (*Gustavson, 1977.*), their contribution to MMR has not been so well defined. Prior to the present study, surveys of MMR populations have not included routine chromosome analysis of all individuals. Karyotyping was done only in individuals suspected of having a chromosome abnormality.

i. Overall prevalence

Einfeld (1984) whose Australian study looked at medical records of 4500 patients with delayed development, found a prevalence of chromosome abnormality of 0.7% in 249 individuals with borderline intelligence, and of 8.4% in 731 with MMR. The majority of these were Down syndrome - excluding this, the prevalence of chromosome abnormality in MMR was 1%.

Hagberg (1981) found 4 out of 91 (4%) Swedish children with MMR were known to have a chromosome abnormality, two of those had trisomy 21.

In *Czeizel's* Budapest study, all children had buccal smears, but chromosome analysis was done only on those suspected of having an abnormality. 3.2% were found to have a chromosome abnormality.

The prevalence of chromosome anomalies in *Blomquist's* Swedish study, which was comparable in size to the present study, was 8%, higher than that of this Southampton study. *Blomquist's* study, however, included 11 children with Down syndrome, and 4 boys with the fragile-X syndrome. Possible reasons for the increased number of mildly

retarded children with these conditions in the Swedish study are discussed below.

Of 166 tested in this survey, 9 (5%) had a major chromosome abnormality. This is a ten-fold increase over the prevalence of chromosome abnormalities found, with less sophisticated cytogenetic techniques, in newborn infants. (*Jacobs, 1974.*)

If we had limited chromosomal analysis in this survey to children with dysmorphic features, or to children with no adverse features in their early background, we should have failed to identify 4.

In 5 of the 6 children identified during the study, there was no indication for chromosomal analysis other than MMR; they were not noticeably dysmorphic. In addition, 4 of these 5 had adverse factors in pregnancy, the perinatal period, or in their social background. Ironically, the one dysmorphic child [59]- 46,XY.t(3;15) - in whom a chromosome abnormality was found, had inherited the translocation from his phenotypically normal mother and maternal grandmother. It is therefore likely to be balanced and unassociated with his retardation or dysmorphic features.

ii. Down syndrome

The present study had the lowest reported prevalence of Down syndrome in children with MMR. Down syndrome cases were considerably more frequent in both the Australian and North Swedish studies. Blomquist's (1981) Swedish study of 171 children with MMR included 11 children with Down Syndrome : the present study, of 169 children, included 2. Furthermore, there was just one case of Down syndrome in the 62 eligible children not included for various reasons (Table III.1) in this Southampton study. Had the study been limited to looking at records as in that of Einfeld, the prevalence would have been 1.3%.

Although in Blomquist's study, where maternal age is discussed, a greater proportion of mothers - 18% - were aged 35 years or more at the time of delivery than in the present study in which 11.3% were 'older' mothers, 5 of the Swedish Down syndrome children were born to mothers under 35 years old; there were none such in the present study. Variation in maternal age is unlikely to be a factor associated with the low prevalence in our study. Data obtained from the Wessex Regional Genetics Laboratory show that at least 53 children were born with Down Syndrome in the Southampton area during the period relevant to the study - 1971-1976. Some of these children may not have survived to school age and some would be admitted to ESN/S schools - but it is still surprising to have found so few in the present study.

iii. The fragile-X syndrome

This has been reviewed in *Section I - 4*. It is now accepted as being second only to Down syndrome as a cause of mental retardation in males. (*Blomquist, 1983*).

The findings in this study of just one doubtful positive fragile-X, subsequently considered not to be significant, in all 166 children tested, does not reflect the prevalence found in other studies. Blomquist's (1983) finding of 5 boys with fragile-X in a population of 110 ESN/M children has already been mentioned *Section I, 4, a*. Webb (1986) looked specifically for fragile-X chromosome in a population of 394 children attending ESN/M schools in Coventry. Of 138 boys tested, 10 showed the fragile-X chromosome; of 94 girls tested, 9 had fragile-X. This prevalence in girls reflected the findings of an earlier Australian study by Turner (1980) of 128 girls with MMR 72 had no physical abnormalities, and were tested for fragile-X. Five of these girls were shown to carry this marker X chromosome.

Hecht (1984) recommends that 50 cells, 10 banded, 40 unbanded, should be checked to detect the presence of fragile-X. In this study 30 cells were examined from each specimen. This may have reduced the level of detection but it is a possible, rather than probable, explanation for the low prevalence of fragile-X in these children. The selection policies of different education authorities could affect the prevalence of certain conditions in school children receiving special education, but this, is speculation. Whatever the reason, it was surprising that no children with fragile-X were found during this survey.

The possible identification of children carrying the fragile-X chromosome was one of the main reasons for undertaking this survey. Families of affected children could be offered genetic counselling; and testing of females at risk of being carriers. This would offer scope for a possible reduction in the overall prevalence of mental retardation. The fact that no children with fragile-X were identified in this survey was disappointing, but screening programmes for the fragile-X chromosome amongst retarded populations should be encouraged - the potential is there!

Recently - within the last few months - the gene for fragile-X has been identified, and gene probe analysis can now be used to identify carriers of the fragile-X with much greater reliability (*Davies, 1991*). It would be of great interest - but not, unfortunately, within the scope of this study, to rescreen the study children for fragile-X by this means. It should not, however, be long before the techniques employed for such gene probe analysis become generally available - with ensuing possibilities for reducing the prevalence of mental retardation.

iv. Sex chromosome aneuploidy

Sex chromosome aneuploidy was found in 3 of the 96 boys (3%): 2 47,XXY. and 1 48,XXYY. All 3 showed the speech problems commonly found in boys with sex chromosome aneuploidy, but all 3 had normal body proportions, no gross dysmorphic features or unduly small testes.

Sex chromosome abnormalities occur in 0.3% of newborn boys. (*Jacobs, 1974.*) The total school population of appropriate age in Southampton during the period of the survey was 11,921. Of these children, about 18 boys should have an abnormal sex chromosome complement. We identified 3. Klinefelter syndrome is thought to reduce the initial IQ potential of an affected individual by 10-20 points. However, a follow-up study of 12 boys aged 16-18 years found to have XXY karyotypes during a neonatal screening programme reported that they had few difficulties with education until secondary school (*Ratcliffe, 1982*). It is therefore possible that problems in the early history and family background were the main factors responsible for the early referral to an ESN/M school of the 2 XXY boys identified in the survey.

The XXYY boy had no adverse features in his history or social environment. The mean IQ of 33 XXYY boys reviewed by *Barlow (1983)* was 62.6; the retardation of our XXYY boy can be reasonably attributed to his sex chromosome aneuploidy. He had poor co-ordination, a short attention span, and impulsive behaviour, which are in keeping with other XXYY boys (*Borgaonkar, 1970, Bloomgarten, 1980*).

The higher prevalence of sex chromosome aneuploidy found in this study, as compared to previous studies, resulted from performing chromosome analysis on every child. As with 3 boys in the study, MMR may be the sole phenotypic effect in childhood of a sex chromosome

anomaly. Early identification of sex chromosome aneuploidy means that the child can be referred for regular paediatric supervision, with possible hormonal therapy. Although hormonal therapy will not affect primary gonadal dysfunction, it can be of benefit both in behavioural disorders and in affecting final body habitus in children with sex chromosome aneuploidy.

b. X-autosome translocations

X-autosome translocations are a relatively rare form of reciprocal translocation. The girl with the karyotype 46,X,t(X;19) fell within the range of borderline intelligence - IQ 74. Mental retardation is not invariable with X-autosome translocations but was present in 6 out of 66 cases reviewed. (Carpenter, 1980). Despite a history of very heavy alcohol intake by her mother during pregnancy, she showed none of the physical signs of the fetal alcohol syndrome, but one cannot exclude this as a contributory factor in her retardation.

c. Deletion in Chromosome 15

The deletion of chromosome 15 found in 1 child is similar to that described in association with the *Prader-Willi syndrome*. (Mattei, 1983) This girl had, apart from her retardation, no features of the syndrome. She had an Apgar score of 4 at 5 minutes after delivery, and was in the special care nursery for a week thereafter, but there was no history of hypotonia or motor developmental delay. She was heavily built, but not unduly obese, and did not have an exceptional appetite. Schwartz (1985) reviewed 15 cases with similar deletions of 15q: while 13 of these were hypotonic, the only feature common to all was mental retardation.

This girl's retardation is probably due, at least in part, to the chromosomal deletion.

d. Maternal age

The two girls with Down syndrome, one of the XXY boys, and the girl with a deletion in chromosome 15, were all born to mothers who might more recently have been offered amniocentesis or chorion villus sampling because of age. At maternal age 38 years [133] the risk of Down syndrome is 1 in 200: by the age of 48 years [111] it has risen to 1 in 11.

The risk of any fetal chromosome abnormality increases with maternal age. Hence, the XXY karyotype in a child [40] born to a 38 year old mother, and the interstitial deletion of chromosome 15 in a child [107], born to a 39 year old mother, may also be related to maternal age.

The availability of prenatal diagnosis to older mothers, with the option of termination for chromosome abnormality found in the fetus, may eventually cause some reduction in mental retardation from this cause. Relatively few births however, - about 11% - occur to women aged 35 years or over, the age group to whom prenatal diagnosis is usually offered. Nor is the uptake of such prenatal diagnosis high in Wessex, the average is between 30 and 40%. Sporadic chromosome anomalies occurring in children born to younger women who are not routinely offered prenatal diagnosis will continue to contribute to mental retardation.

There is some evidence at present to suggest that maternal levels of alpha-feto protein, human chorionic gonadotrophin and possibly oestriol, at sixteen weeks gestation, may be used to screen for Down syndrome (Wald, 1988). If current trials prove satisfactory, women of all ages found to be at risk on this biochemical screening could be offered amniocentesis and fetal karyotyping. It is thought that such screening would have the potential to reduce Down syndrome births by 60%.

Four of the children with de novo chromosome aberrations, [7,106,21,35] were born to mothers aged 25 years or less. Short of offering prenatal chromosome testing to all pregnant women - which is not feasible - there is no way in which these chromosome abnormalities could have been predicted.

The current use of prenatal diagnosis of the fetal karyotype is unlikely to reduce the prevalence of mental retardation to any significant extent. It will be interesting to see how maternal biochemical screening for Down syndrome develops.

f. Benefits of diagnosis of chromosome abnormalities

Although 8 study children had chromosome abnormalities probably associated with their retardation, these chromosome abnormalities had all arisen de novo. The recurrence risk, apart from that already associated with maternal age in the four older mothers, was low. Identification of these chromosome abnormalities did not therefore have a potential for reducing further cases of mental retardation via genetic counselling: as already discussed, this was particularly so in that no cases of fragile-X syndrome were found.

Identification of children with chromosome abnormalities, however, in the routine karyotyping of the survey was helpful in 3 ways.

a) The 2 boys found to have *Klinefelter* syndrome and the XYY boy were referred to a paediatrician for supervision and possible hormonal therapy.

b) Parents found it helpful, in dealing with their child's retardation, to have a specific diagnosis.

c) Although the balanced translocation in [59] was probably not associated with his retardation, it was familial. There is a risk that carriers of such a balanced translocation - including the study

child - could produce children with an imbalanced form which would lead to retardation. Chromosome analysis was offered to family members : the risks were explained to those found to carry the translocation, with the offer, where appropriate, of prenatal diagnosis. Hence the finding of a balanced translocation in the study child was of potential benefit in the prevention of mental retardation elsewhere in his family.

CONCLUSION

There is potential for finding chromosome abnormalities - especially fragile-X - in children, both boys and girls, with MMR. This study of an unselected series of 166 children with MMR has detected chromosome abnormalities of 5%.

I suggest that consideration be given to karyotyping all children referred to ESN/M schools.

PRENATAL MEDICAL FEATURES

2. GENETIC SYNDROMES

All children suspected of having a genetic syndrome were also seen by Dr N.R.Dennis for confirmation of the diagnosis.

Results

a. Five study children had genetic syndromes of recognised association with mental retardation.

Two syndromes were Mendelian, 3 non-Mendelian. Details are given in Table V.4.

b. Syndromes in 2 children were diagnosed prior to the survey.

The child [54] with *Rubenstein-Taybi syndrome* was diagnosed at birth when his broad, radially deviated thumbs were noted.

The child [63] with *Sotos syndrome* was seen by a clinical geneticist one year prior to the survey - he had been referred because of developmental delay. His mother also had features of this autosomal dominant condition - large birthweight, facial features of prominent eyes and a long jaw: she had also attended an ESN/M school.

TABLE V.4

Genetic syndromes, with other features, in 5 out of 169 ESN/M children.

Case No.	Mendelian		Non-Mendelian		104
	63	76	154	58	
Syndrome	Sotos	Aarskog	Rubenstein-Taybi	Prader-Willi	Cohen
IQ	58	68	61	78	75
Maternal age at birth	36	19	26	28	33
Paternal age at birth	41	26	29	30	33
Birth weight (g)	2850	3200	2640	2438	4210
Prenatal features	-	-	-	-	Hypertension
Perinatal features	Born at 34 wks gestation. Hyaline membrane disease.	-	Jaundice	Hypotonia	-
Early motor delay	+	-	+	-	-
Early speech delay	+	-	+	-	-
Dysmorphic features	Macrocephaly. Hypertelorism. Long, narrow mandible. High arched palate Advanced bone age.	Short stature. Hypertelorism. Epicanthic folds, clinodactyly R and L. Interdigital webbing. Shawl scrotum. Cryptorchidism	Beaked nose, long nasal septum. Broad thumbs with radial deviation. Cryptorchidism.	Marked obesity, excessive appetite. Small hands and feet. Almond-shaped eyes.	Prominent incisors, Lax joints, R. Simian crease. Moderate obesity. Mild hypotonia.
Home background	Average	Average	Good	Poor	Average
Comments	Autosomal dominant Mother-probable Sotos;ESN/M	X-linked. Mother-short; hypertelorism. operation for R.ptosis Grandmother-short, R.ptosis. Brother-short, bilateral ptosis.	-	Father-Illiterate	Mother-ESN/M

c. Three children were diagnosed as having genetic syndromes in the course of the survey.

One syndrome was Mendelian - *Aarskog*, [76], which has an X-linked inheritance. This child showed the cardinal features - hypertelorism, short stature, shawl scrotum - of this condition, and had the ptosis and undescended testes commonly also associated. (*Aarskog*, 1970)

The mother and maternal grandmother of this study child both had short stature and unilateral ptosis and were of normal intelligence. One of his 2 brothers - neither of whom was retarded - had bilateral ptosis, requiring operative correction, and was short. The other brother had no ptosis and was of normal height.

Prader-Willi syndrome was diagnosed in a girl [58], who had been hypotonic in the neonatal period, was markedly obese - especially in the lower abdomen and thighs - had disproportionately small hands and feet, and who had a voracious appetite. Her chromosomes were normal.

Another girl [104], whose main dysmorphic feature was exceptionally large incisor teeth, but who also had lax joints, mild hypotonia, and moderate obesity, was diagnosed as having *Cohen syndrome*.

COMMENTS

a. The genetic syndromes analysed in 5 study children all have a recognised association with mental retardation. The degree of retardation varies from severe - with IQs of 20 or below - to borderline intelligence in *Sotos* (*Sotos, 1964;*), *Rubenstein-Taybi* (*Rubenstein, 1963;*), *Cohen* (*Cohen, 1973; Kousseff, 1981;*), and *Prader-Willi* (*Hall, 1972*) syndromes. In *Aarskog syndrome* (*Aarskog 1970; Van de Vooren, 1983*) the degree of retardation is less marked, with an intelligence range from that of MMR to the lower ranges of normal.

b. The prevalence (2.9%) of recognised genetic syndromes in children in this survey is similar to that found in European studies. Genetic syndromes were present in 2 out of 91 (2.2%) Swedish children with MMR studied by *Hagberg (1981)* and in 29 out of 1,060 (2.7%) children with MMR in Budapest studied by *Czeizel (1980)*. *Blomquist (1981)* identified syndromes in 5 out of 171 (2.9%) children with MMR. In all these surveys, as in the present one, children were examined by a clinician.

c. Relatives of 2 children with syndromes of Mendelian inheritance had relevant features.

The child with *Sotos syndrome* appeared to have inherited it from his mother.

In *Aarskog syndrome*, female carriers of the gene may have mild manifestations. The unilateral ptosis in the mother and maternal grandmother may be due to Lyonisation. One brother with normal stature and no ptosis, is unlikely to have inherited the gene. The other brother, who was short, and had bilateral ptosis, had probably inherited the gene - but did not have mental retardation.

d. No parents or siblings of the three children with syndromes thought to be of sporadic occurrence, - Rubenstein-Taybi, Prader-Willi, Cohen - had any relevant dysmorphic features.

e. Two of these children with sporadic syndromes had a parent who had educational problems. This parental history may have contributed to the ESN/M referral.

f. Chromosome anomalies, mainly deletions, have been reported in the proximal part of the long arm of chromosome 15, in q11-q13 in association with Prader-Willi syndrome (*Cassidy, 1984; Mattei, 1983; Ledbetter, 1982.*) Such deletions have been found in up to half of reported cases of Prader-Willi syndrome. The finding of a normal karyotype in the study child with Prader-Willi syndrome does not preclude the diagnosis. Recently a proportion of individuals with Prader-Willi syndrome who do not show this deletion have been found to have maternal disomy of chromosome 15 (*Gavranich, 1989*). Techniques which have led to this finding were not available at the time of the study, and such testing was not done on the study child.

g. Three children had genetic syndromes diagnosed in the course of the study. Dysmorphic features in genetic syndromes may be "soft", and have to be looked for.

I would recommend careful physical examination of children in ESN/M schools by school medical officers, looking especially for minor dysmorphic features. Referral to a paediatrician or geneticist should be considered if 3 or more dysmorphic features are found, or if a genetic syndrome is suspected.

h. As with chromosome abnormalities, diagnosis of a genetic syndrome, with a name attached to it, may help parents to come to terms with mental retardation in a child.

In this respect, careful screening of the ESN/M children for genetic syndromes can be of value.

i. Many of the recognised syndromes are sporadic, with a low recurrence risk. Such syndromes do not offer scope for a possible reduction in cases of mild mental retardation, either in their families or in the community.

In those syndromes known to have Mendelian inheritance, genetic counselling should be offered to the parents, and to the children themselves when they reach reproductive age. However, parents seen after the diagnosis of a genetic syndrome of a child aged 7 or 8 years - the usual age for ESN/M referral - may well have already completed their families, and a person afflicted with a genetic syndrome is unlikely to be deterred by a possible risk of producing a similarly affected child. Also, in many Mendelian genetic syndromes where mental retardation may occur, the extent of retardation, even within the same family, can vary. This uncertainty relating to an affected child's eventual intellectual level would severely limit the use of prenatal diagnosis, even if this were available, and for the majority of genetic syndromes associated with MMR, prenatal diagnosis is not yet feasible.

Hence, while diagnosis of genetic syndromes contributes to our knowledge of the aetiology of MMR, such diagnoses are unlikely to contribute to any significant reduction in the prevalence of MMR in the population.

TABLE V.5

Malformation of the central nervous system, with other features,
in 5 out of 169 ESN/M children.

Case No.	155	151	68	122	134
	Hydrocephalus	Hydrocephalus	Microcephaly	Microcephaly	Microcephaly
IQ	65	71	77	60	55
Maternal age at birth	32	26	23	28	27
Paternal age at birth	25	40	24	28	26
Birth weight (g)	2620	2730	3910	N/A	2150
Prenatal features	-	Mild toxemia	-	-	Pre-eclampsia
Perinatal features	Born at 34 wks gestation. Apgar 6 at 5 mins. Respiratory distress syndrome. Jaundice.	Neonatal twitching	Jaundice	-	-
Early motor delay	-	-	-	+	-
Early speech delay	+	-	-	++	++
Dysmorphic features	OFC > 97th centile Long narrow face.	-	Ridged coronal and sagittal sutures. Prominent broad base to nose. Small mouth. Bilateral clinodactyly. Broad tips to thumbs. Winged scapulae.	-	-
Home background	Average	Average	Average	Average	Poor
Comments	Hydrocephalus diagnosed at 7 wks. Not treated surgically.	Diagnosed at 4 wks. Shunt inserted-L. high tone hearing loss.	Mild R. spasticity Enuretic	Born in India. Birth details unavailable.	Father ESN/M

PRENATAL MEDICAL RISK FACTORS

3. MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

Results

a. Five survey children had major malformations of the central nervous system. (Table V.5)

Two boys were found to have *hydrocephalus* soon after birth : 3 girls had *microcephaly*.

b. Both boys with hydrocephalus had a normal OFC at birth. One child [155] was born at 34 weeks' gestation, was slow to establish respiration and was in the special care unit for 3 weeks. When seen at 7 weeks of age, OFC was well over the 97th centile. He was kept under supervision and the hydrocephalus appeared to settle spontaneously. When seen, his OFC was 59.2 cm, >97th centile for his age.

Hydrocephalus was diagnosed in the other boy [151] when he was referred with a clicking hip at the age of 4 weeks. He had been noticed to have neonatal twitching. His OFC at birth was 33cm; a month later it was 42.5cm., well above the 97th centile. He was treated surgically : the catheter, which had been removed and lengthened as necessary, was still in place when seen. His OFC was 53.6cm., just above the 50th centile.

c. Microcephaly had been identified in 2 girls prior to the survey, during hospital investigation of developmental delay.

One child [68] had a normal delivery, but was described by the mother as a 'floppy and unresponsive' baby. She was seen at the age of 6 months, when she was found to have microcephaly. This child had

several dysmorphic features which did not fit any recognised syndrome.

The other child [122] had been born in India and no details of her birth were known, although she was said to be very small at birth. She was investigated because of gross global delay at the age of 4 years, and was found to be microcephalic - when seen, her OFC was 47cm. - well below the 3rd centile, and disproportionate to her height and weight, which were on the 25th centile. She had no dysmorphic features. There was no known consanguinity in her parents; she had five sisters, all of normal intelligence.

The third girl [134] with microcephaly had not had any hospital investigation. There had been no motor delay, but she was very late in speaking and still, when seen, had poor speech. She had a flat occiput, her OFC was well below the 3rd centile; her height and weight were just below the 50th centile. Her father had received ESN/M education; there was no known parental consanguinity. She had one sibling, a younger sister who was not evidently retarded.

COMMENTS

a. Follow-up studies of children with infantile hydrocephalus have shown that the condition may be associated with low intelligence. *Hagberg (1962)* found 7 out of 26 children who had had infantile hydrocephalus to have IQ scores between 70-90. *Badell-Ribera (1966)* showed that performance scores were reduced in children who had had early hydrocephalus. Although early hydrocephalus does not invariably lead to diminished intelligence, the association is recognised. It is probable that hydrocephalus had contributed to ESN/M referral in these two boys; neither had any familial retardation.

b. *Blomquist (1981)* found hydrocephalus in 2 out of 71 Swedish children with MMR, - a prevalence similar to that of the present study. Two other comparable surveys of children with MMR - that of *Czeizel (1980)* and of *Hagberg (1981)* make no specific mention of hydrocephalus.

c. There was no family history to suggest that the X-linked form of hydrocephalus was operating in the family of either boy with hydrocephalus, and neither had the adducted thumbs often associated with this condition.

d. A link between microcephaly and mental retardation is accepted. *Martin (1970)* looked at 202 children with microcephaly; 7.5% were not retarded. *O'Connell (1965)* found mental retardation in 133 out of 134 children whose head circumference was reduced by more than 2 SD below the norm.

One study child [77] had dysmorphic features which suggested a prenatal disruption of development; her microcephaly was probably part of a wider spectrum of impaired morphogenesis.

Another girl, [134] with no abnormal physical features apart from microcephaly, had a history of familial retardation. Her IQ was fairly low at 55; her younger sister was not evidently retarded. The microcephaly may have been associated with a reduction in IQ from the borderline range.

The third girl [122], again with isolated microcephaly, had no history of familial retardation. Her microcephaly could well have had a prenatal origin - she was known to have been very small at birth.

e. Although none of these 3 microcephalic girls had similarly affected siblings, and there was no known parental consanguinity, the possibility of autosomal recessive inheritance cannot be excluded - especially in the 2 girls with no other abnormal physical features.

There is at present, no way of identifying cases of microcephaly which are due to autosomal recessive genes. Where isolated microcephaly has been found, parents may be offered careful scanning of the head size in any future pregnancy, but the diagnosis may not be confirmed until the pregnancy is well advanced.

f. Scope for reduction in the prevalence of microcephaly and hydrocephalus as aetiological agents in MMR is limited. Microcephaly severe enough to be picked up on ultrasound scanning in early pregnancy would carry an unfavourable prognosis of severe, rather than mild retardation. Milder degrees of microcephaly, which might be associated with mild mental retardation would not be so readily diagnosed in utero - it is doubtful if such a diagnosis could be made with certainty before the last trimester.

Knowledge of hydrocephalus developing in late pregnancy can alert paediatricians to the possibility of early intervention - thus perhaps reducing any risk of mental retardation. Hydrocephalus, however, may not develop till after birth - as in the two boys in this survey.

PRENATAL MEDICAL RISK FACTORS

4. INBORN ERROR OF METABOLISM

Results

a. One survey child [115] was already known to have an inborn error of metabolism - congenital adrenal hyperplasia. (Table V.6).

At birth this girl was noted to have fused labia and clitoral hypertrophy. Neonatally she was very jittery, with marked twitching. A diagnosis of congenital adrenal hyperplasia was made on day 5, but control of the salt-losing state was difficult to establish, and was erratic for the first 3 months. The child had a major convulsion with opisthotonos when aged 8 weeks, and was noted after this to have a left facial palsy. She remained irritable for some months. At 7 months of age she had poor head control, and a bone age equivalent to 3 months. At one year she was noted to be Cushingoid and hirsute. She had no further major crises, but control of the condition was somewhat unstable for the first few years.

The parents were first cousins. Two younger siblings both had congenital adrenal hyperplasia diagnosed at birth, but have been well-controlled, and are not retarded.

TABLE V.6

Inborn error of metabolism, identified in 1 out of 169 ESN/M children.

Case No.	115
Condition	Adrenal hyperplasia
IQ	64
Maternal age at birth	35
Paternal age at birth	37
Birth weight (g)	3470
Prenatal features	-
Perinatal features	<u>Neonatal twitching</u> , salt loss difficult to control.
Early motor delay	+
Early speech delay	+
Dysmorphic features	Fused labia, enlarged clitoris at birth. L. congenital glaucoma. Hirsute, Cushingoid appearance.
Home background	Average
Comments	Parents - first cousins. Crisis with opisthotonos at 2 months followed by left facial palsy.

b. Biochemical screening

i. *Urine*

Children

Collecting urine samples in school from the children proved to be unexpectedly difficult, especially in some of the girls; it caused more problems than taking blood samples.

In 6 girls [49, 80, 86, 97, 115, 122] urine samples could not be obtained on 2 successive attempts.

NO major abnormalities were found in samples screened for the remaining 163 children.

One child [21] was found to have protein in his urine. The family doctor was informed, and a 24-hour urine collection organised. The total output of urinary protein in this sample was <1 gm. This result was not felt to merit further investigation.

Mothers

All 154 mothers seen provided urine samples. In 3 children [62,98,123] the mother was not involved in the care of the child, did not live locally and was not seen.

Ten mothers had 2 children in the survey, one had 3.

NO abnormal metabolites were found in the urine samples from 137mothers.

Traces of blood were found in the urine of 17 mothers known to be menstruating when the sample was provided.

*ii. Blood*Children

Blood samples for analysis were not obtained from 3 children.
(Section V, A, 1a)

In all 166 children tested -

screening for phenylketonuria and
hypothyroidism were NEGATIVE.

Mothers

Of 154 mothers in the survey, blood samples for amino acid chromatography were obtained from 148.

Two mothers were unwilling to provide a blood sample.

In four mothers venipuncture was unsuccessful.

None of these 6 mothers had more than one child in the survey. The lack of a maternal blood sample was not thought to be sufficient grounds to exclude these families from the survey.

Figure 1 shows a typical amino acid profile and print out from the Rank-Hilgar spectroscope.

Glutamic acid and cystine run very closely with other peaks.

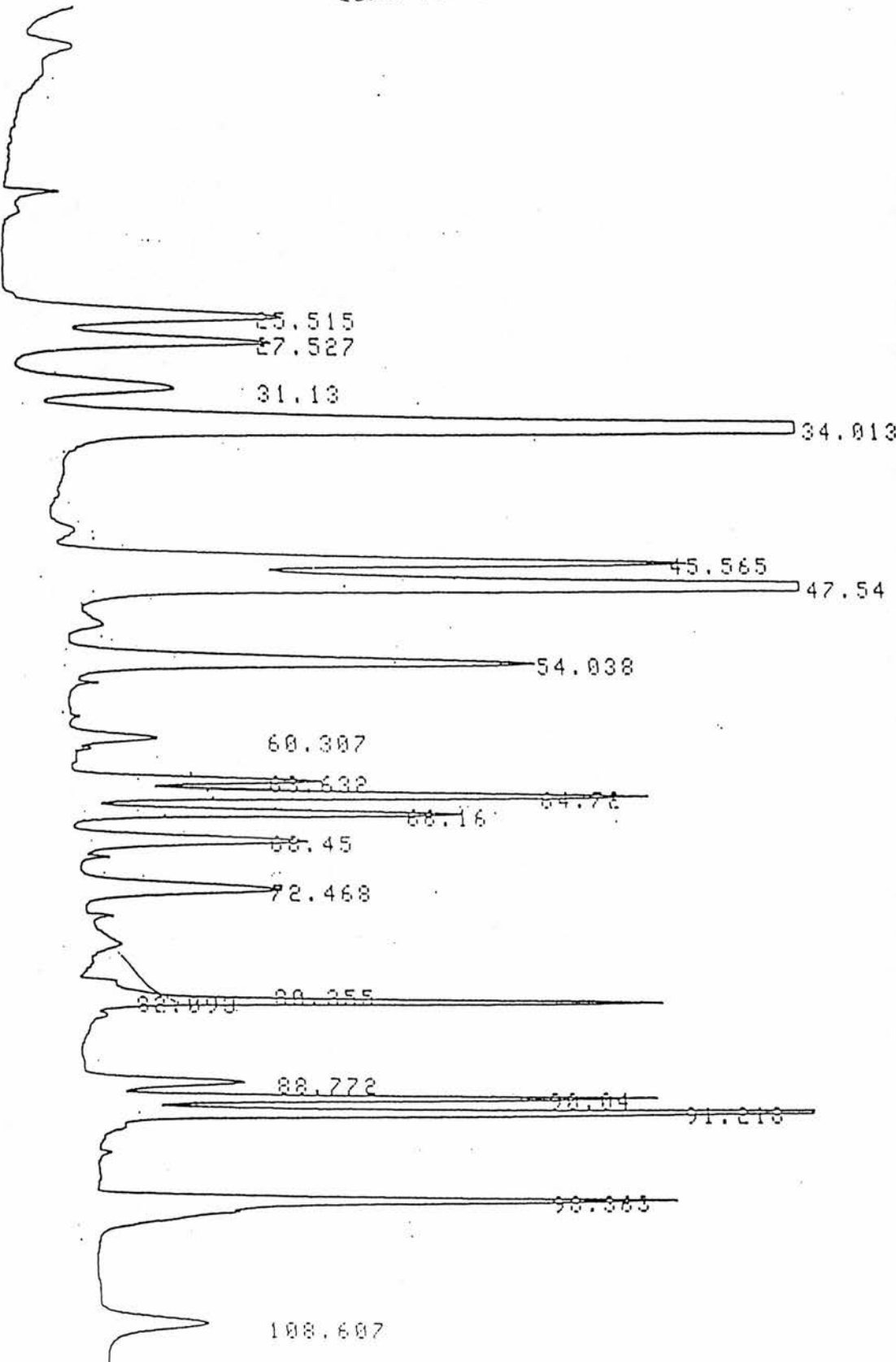
Glutamic acid could not be quantified in 67 mothers.

Cystine could not be quantified in 54 mothers.

NO abnormalities were found.

The quantitative amino acid analyses did not show abnormal serum concentrations of the amino acids tested in any of the 148 mothers who were screened.

Case 116.



C-R2AX

FIGURE 1 - Graph and print-out of maternal amino-acid analysis - case 116.

Case 116

CHANNEL 1
 SAMPLE NO 0
 REPORT NO 6
 IS WT 100

FILE 1
 METHOD 43
 SAMPLE WT 100

PKNO	TIME	AREA	MK	IDNO	CONC	NAME
1	25.515	1376201		3	126.5397	THR
2	27.527	1200899	V	4	108.73	SER
3	31.13	753629		5	71.5562	GLA
4	34.013	7073366	V	6	695.9909	GLM
5	45.565	2680062		7	209.2211	GLY
6	47.54	5632039	V	8	534.2933	ALA
7	54.038	1969039		10	198.4806	VAL
8	60.307	252396		11	18.7235	MET
9	63.632	682988		12	69.2234	ILEU
10	64.72	1672925	V	13	134.188	LEU
11	66.16	1110949	V	1		NLEU
12	68.45	857123		14	63.3391	TYR
13	72.468	860646		15	63.2919	PHE
14	80.355	214031				
15	82.093	1328131	V	17	102.0861	HIS
16	88.772	521251		18	45.9264	TRY
17	90.04	1259502	V	19	106.5373	ORN
18	91.218	2021987	V	20	165.3291	LYS
19	98.363	2301924				
20	108.607	563877		21	56.5815	ARG
TOTAL		34332948			2770.0368	

COMMENTS

a. Congenital adrenal hyperplasia is not, per se, associated with mental retardation. In the study child, however, the difficulty in stabilising the condition led to an acute episode at 2 months of age, with overt neurological signs. She had delayed development - with poor head control and retarded bone age at 7 months of age. It is reasonable to attribute her mental retardation to the sequelae of congenital adrenal hyperplasia.

b. Biochemical disorders in children with MMR.

Surveys of new-born infants and young children for amino acidopathies and organic acidurias have been unrewarding. *Smith, (1975)* and *Chalmers (1980)* concluded that such investigations should be limited to infants with acute unexplained illness, and that

"mental handicap or developmental delay were unrewarding pointers to the possible existence of an inborn error of metabolism"

However, *Krieger (1982)* screened 1180 mentally retarded children referred for hospital investigation and found 81 inborn metabolic errors. He recommended biochemical screening in the investigation of unexplained mental retardation.

Einfeld (1984) in his study of the medical records of 4500 individuals with developmental delay in Australia found 25 out of 731 (3%) with MMR to have metabolic defects. In *Czeizel's (1980)* Budapest study of 1080 children with MMR, inborn errors of metabolism were found in 2.5%. *Hagberg (1981)* in his study of 91 retarded Swedish children, mentions that one child in the IQ range 71-75 had leucine intolerance. *Blomquist (1981)* found one child to have phenylketonuria, another with hypothyroidism, out of 171 children with MMR. Just one child (0.6%) in our study had an inborn error of metabolism - a prevalence lower than that of the Australian and Hungarian studies. Although this survey did not reveal any children

with undiagnosed metabolic errors, it is, however, worth remembering that in some of the amino acidopathies, clinical expression may be limited to MMR. Where MMR is unexplained, and especially where a sibling is similarly affected, biochemical investigation should be considered.

c. Biochemical disorders in the mothers of children with MMR

As mentioned above, the design of the study included a search in the children's mothers not only for undiagnosed PKU, but for other amino acidopathies; this search gave negative results.

The association of maternal PKU, diagnosed or undiagnosed, with mental retardation in offspring, is well established, (*Mabry, 1966; Perry, 1973*) and, although no mothers in the survey were affected, this is something that should be borne in mind when investigating children with MMR. In Wessex, notifications to the PKU register in 1974-1978 were 17.0 per 100,000 live births. Against this background incidence there are likely to be a number of women with undiagnosed PKU, who were born prior to routine screening. Where no cause is evident for a child's retardation, it would seem advisable to check for maternal PKU - especially if more than one child in a family is retarded, or if microcephaly, a frequent feature in such affected children, is present.

The study provided no evidence of involvement of any other undiagnosed maternal amino acidopathies in mental retardation, and there do not appear to be any grounds for including a search for maternal biochemical defects, other than PKU, in the investigation of children with MMR.

I would recommend, however, that in children who have MMR with no apparent cause, screening should be done for

- a) An amino acidopathy in the child.
- b) Undiagnosed PKU in the mother.

PRENATAL MEDICAL RISK FACTORS OF ENVIRONMENTAL ORIGIN

Results

a. Three study children had environmental prenatal features probably associated with their mental retardation. (Table V.7).

b. The girl [74] with toxoplasmosis was small-for-dates at term, but toxoplasmosis was not diagnosed until she was 9 months old, when choroidal pigmentation was seen.

Her toxoplasmosis titre was >1:2,000 : the mother's was 1:256.

This child had severe retinal scarring, and was registered as blind.

c. *Syphilis* was diagnosed, as a recent new infection in the mother of one boy [149] at 14 weeks' gestation and was treated with *benzyl penicillin*. Her syphilis serological tests remained positive. At birth the baby's fluorescent trepanomal antibody test was IgG +ve, IgM -ve.

Dysmorphic features when he was seen included bat ears, and skull and facial asymmetry.

d. The mother of [98] was a known alcoholic, drinking more than half a bottle of whisky each day.

The child had intrauterine growth retardation, weighing 1980gm. when born at 38 weeks' gestation.

When seen, she had mild microcephaly, short palpebral fissures, mid-face hypoplasia, thin upper lip and short stature. Her appearance (Appendix A) was in keeping with that of *fetal alcohol syndrome*.

This child had been raised in poor home circumstances by her father.

TABLE V.7

Non-genetic prenatal features in 3 out of 169 ESN/M children, with other findings.			
Case No.	74	149	98
Condition	Toxoplasmosis	Syphilis	Alcohol fetopathy
IQ	58	69	70
Maternal age at birth	28	26	27
Paternal age at birth	27	27	33
Birth weight (g)	2610	3685	1930
Prenatal features	-	<u>Syphilitic infection at 14 wks. treated with penicillin.</u>	<u>Excessive alcohol intake. IUGR noted at 32 wks.</u>
Perinatal features	-	-	Antepartum haemorrhage. LSCS for placenta praevia.
Early motor delay	+	-	-
Early speech delay	+	-	-
Dysmorphic features	Intracranial calcification. Severe retinal scarring.	Bat ears. Asymmetric skull - flattened on L. Dermatoglyphics - 9 whorls.	Small stature (3rd centile) OFC-2 SD. High front hair line. short palpebral fissures. Maxillary hypoplasia. Thin upper lip.
Home background	Average	Average	Poor
Comment	Diagnosed when 9 months old. Precocious puberty (7 years). Epilepsy from 4-9 years.	At birth-syphilis serological tests-IgG raised, IgM low.	-

COMMENTS

a. Two of the 3 children in this group had physical and clinical features which corroborated the link between their mental retardation and the adverse prenatal factors: in the third child [149] the link was inferred.

b. The girl with toxoplasmosis had a raised titre (>1.2000) at 9 months of age. Her intracranial calcification, retinal scarring and subsequent epilepsy are evidence of the damage wrought by the infection. Mental retardation has been found in 89% of children infected with toxoplasmosis in utero. (*Remington and Desmonts, 1983*).

c. The fetal alcohol syndrome (FAS) is a well recognised entity (*Jones, 1983; Frias, 1982.*), although the features are less dramatic than toxoplasmosis. The study child diagnosed as having this syndrome had the typical physical features - (intrauterine growth retardation, small head, mid-face hypoplasia, short palpebral fissures) - and her mother was a known alcoholic. Affected children are mildly retarded -IQ 63 on average; our study child had an IQ of 70.

d. Alcohol fetopathy was found in just 1 -(0.6%)- of the study children.

By contrast, *Hagberg (1981)*, in a similar study of 91 ESN/M Swedish schoolchildren found FAS in 6%. In the USA, FAS is thought to be the third most common cause of mental retardation arising from prenatal causes. (*McDonald, 1986*). These higher estimates of the prevalence may reflect cultural trends but it is interesting to note that *Blomquist (1981)* found no confirmed cases of FAS in 171 ESN/M children in a rural part of N Sweden. *Einfeld, (1964)* reviewed 4500 Australian children with all grades of mental retardation but

biased towards more severe grades. He does not, in his report, specify FAS as such, but found evidence of prenatal teratogens - presumably including alcohol - in 0.3%. *Czeizel (1980)* mentions that FAS was suspected in some of the 1080 children with MMR in his survey, but no unequivocal diagnosis was made.

The children in this present study had a detailed physical examination : no other children had features suggestive of FAS.

The present study is relatively small, but results do not suggest that excess alcohol intake by mothers is a major cause of MMR in Great Britain.

e. The mother of child [149] acquired a syphilitic infection in early pregnancy, which was diagnosed and treated at 14 weeks' gestation with benzyl penicillin. The child had no evidence of active infection at birth - the raised IgG titre indicated passive antibody transfer, the IgM titre was low. Nor were there any of the physical stigmata - such as peg-shaped teeth, saddle nose - of congenital syphilis. The treatment of the mother, however, after 12 weeks, cures, but does not prevent, fetal infection with *trepanoma pallidum* - (*Remington and Klein, 1983.*) and the adverse effects on mental development of syphilitic infection in fetal life, are well known (*Berg, 1959; Wiggelinkhuizen, 1980*).

Thus, although there was no active infection at birth, the mental retardation in this child could be associated with the maternal syphilis in early pregnancy.

f. *Hagberg (1981)* did not find any evidence of prenatal infection in the 91 ESN/M children he studied. *Czeizel (1980)* found 31 out of 1080 (0.8%) children with MMR had had a recognised intrauterine infection, and in *Blomquist's (1981)* study there were 2 out of 171 (1.1%) - a prevalence similar to that of the present study, in which

2 out of 169 (1.2%) children were affected. Einfeld's 1984 Australian study identified 1.8%. This slight increase over the present study may reflect the inclusion in the Australian study, of children with both MMR and SMR in the figure for prevalence of prenatal infection.

SECTION V - MEDICAL FEATURES OF PROBABLE AETIOLOGICAL SIGNIFICANCE

PERINATAL FEATURES

Collection of data

Study Population

1. Information about the perinatal histories of the children is based on details obtained from the mothers and supplemented with information from hospital records obtained directly for children born locally and by written request for children born elsewhere. (*Section IV, 1, 2.*)

2. Obstetric hospital records were not available for 28 children. In none of those 28 did the mothers give a history of perinatal problems. Those records that were seen were correlated closely with the mothers' histories, and it is unlikely that by relying on the birth details given by these 28 mothers, any children with perinatal asphyxia have been overlooked.

3. Twenty-one children had moved to Southampton district since birth. One child [122] was born in India and had no birth records. Forty (24%) children were delivered in maternity units under the supervision of family doctors. Six (3.5%) had been born at home.

The place of birth, availability of records and Apgar scores, and incidence of perinatal stress, are given in Table V.8.

TABLE V.8

Birth information for the 169 study children.

Place of Birth		Records available	Apgar scores	Perinatal stress recorded
Local general hospital	109	109	92	32
Local GP maternity unit	35	24	14	6
Non-local general hospital	14	8	8	2
Non-local GP maternity unit	5	2	2	0
Home confinement	6	0	0	1
Totals	169	141	116	41

4. Children in the survey were born between 1971 and 1976, when fetal monitoring still depended largely on the use of the fetal stethoscope, and neonatal supervision of 'at risk' babies was not so intense or detailed as it is now. Information in case notes was sometimes sparse, and Apgar scoring was not done routinely.

Control population

Perinatal features in index children with no major prenatal or postnatal features were compared with those of their unaffected siblings (attending 'normal' schools) who acted as paired controls. The control sibling was defined as the child nearest in age to the index patient. Those index patients with no siblings attending normal schools were left out of the comparison. As with the study children, relevant hospital records were checked for perinatal details of the control children.

Results

Perinatal features of probable aetiological significance were identified in 46 study children.

Table V.9 summarises these findings.

TABLE V.9

Perinatal features of aetiological significance
in 46 out of 169 ESN/M children.

Fetal distress	10
Blue and limp at birth	4
Apgar score <7 at 5 minutes	16*
Twitching in the first week of life	5
Cyanotic episodes in the first week of life	11

* includes 3 children with prenatal aetiology.

includes 2 children with prenatal aetiology.

Details of each case are given in *Table V.10*. Children in this group have not been considered individually in the text.

TABLE V.10

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.

Case No.	Fetal distress N=10					
	43	56	75	78	119	120
Sex	M	M	M	F	F	F
IQ	-	-	69	57	73	63
Mode of delivery	High forceps	High forceps	High forceps	High forceps	High forceps	High forceps
Gestation (weeks)	41	38	43	40	41	40
Birth weight (g)	2150	3610	4360	3260	3230	2700
Other medical features of probable significance	-	-	-	-	-	-
Other medical features	Cleft lip/palate. Poland's anomaly. IUGR. Small stature.	-	Hyperemesis	Toxaemia	-	Small stature
Home background	Average	Poor	Average	Poor	Poor	Poor

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.				
Case No.	Fetal distress N=10			
	141	144	147	150
Sex	F	M	M	F
IQ	60	84	80	60
Mode of delivery	High forceps	High forceps	High forceps	Caesarean section
Gestation (weeks)	41	40	41	42
Birth weight (g)	3740	3835	3780	3713
Other medical features of probable significance	-	-	-	-
Other medical features	Febrile convulsions Behaviour problems	Hyperemesis, Toxaemia	Threatened abortion at 12 wks.	Hyperemesis; Debendox from 12-30 wks. Behaviour problems
Home background	Average	Good	Average	Good

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.				
Case No.	Blue/Limp at birth N=4			
	18	52	92	143
Sex	M	M	M	F
IQ	61	72	71	71
Mode of delivery	Spontaneous	Spontaneous	Spontaneous at home	Breech-assisted
Gestation (weeks)	33	34	41	38
Birth weight (g)	2324	2014	2780	2530
Other medical features of probable significance	-	-	-	-
Other medical features	-	-	Dysmorphic features	Bleeding 2nd-4th month of pregnancy. Toxaemia.
Home background	Poor	Poor	Average	Average

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.					
Case No.	Apgar score <7 at 5 minutes N=16				
	11	31	40	82	90
Apgar score	6	4	5	4	4
Sex	M	M	M	M	M
IQ	83	60	76	58	52
Mode of delivery	Assisted breech	Spontaneous- cord round neck.	Spontaneous	Emergency Caesarean section- Prolapsed cord	Elective Caesarean section
Gestation (weeks)	40	42	36	33	40
Birth weight (g)	2610	3790	2182	1680	2940
Other medical features of probable significance	-	-	<u>47,XXY</u>	-	-
Other medical features	-	Hyperemesis, Incoordination	Toxaemia	Twin pregnancy	Coarse facial features: early failure to thrive.
Home background	Poor	Good	Poor	Poor	Average

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.					
Case No.	Apgar score <7 at 5 minutes N=16				
	94	97	101	107	109
Apgar score	6	6	4	4	6
Sex	M	F	M	F	M
IQ	61	65	73	66	70
Mode of delivery	Assisted breech	Low forceps	Spontaneous- cord round neck	Assisted breech	Emergency Caesarean section
Gestation (weeks)	40	40	34	42	37
Birth weight (g)	2070	3430	2070	2780	3110
Other medical features of probable significance	-	-	-	<u>46,XX,del 15q</u>	-
Other medical features	Small stature, IUGR	Oral contraception for first 3 months of pregnancy	Incoordination Epilepsy Behaviour problems	Toxaemia	Toxaemia
Home background	Average	Poor	Average	Average	Average

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.						
Apgar score <7 at 5 minutes N=16						
Case No.	136	139	148	153	155	156
Apgar score	6	6	5	2	6	6
Sex	F	M	M	M	M	M
IQ	64	52	63	73	65	67
Mode of delivery	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Elective Caesarean section
Gestation (weeks)	40	42	37	39	34	40
Birth weight (g)	3300	3180	2600	2640	2620	3175
Other medical features of probable significance	-	<u>Apnoea at 3 wks old</u>	-	-	<u>Hydrocephalus</u>	-
Other medical features	-	Behaviour problems	Mild spastic quadriplegia	-	Neonatal jaundice	Incoordination
Home background	Poor	Good	Average	Average	Average	Poor

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.					
Case No.	Neonatal twitching N=5				
	48	115	118	132	151
Sex	M	F	F	M	M
IQ	70	64	61	71	71
Mode of delivery	Spontaneous	Spontaneous	Spontaneous	Low forceps	Spontaneous
Gestation (weeks)	40	41	35	40	40
Birth weight (g)	4309	3470	2636	3530	2730
Other medical features of probable significance	-	<u>Congenital adrenal hyperplasia (CAH):</u> poor salt control with fits.		-	<u>Hydrocephalus</u>
Other medical features	Epilepsy age 3 yrs; on Phenytoin	Ambiguous genitalia Hirsute: Left facial palsy.	Fits in first few weeks of life-none since	-	-
Home background	Average	Average	Average	Average	Average

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.						
Case No.	Neonatal cyanosis N=11					
	2	3	9	23	41	125
Sex	F	F	M	M	M	M
IQ	81	69	85	73	-	85
Mode of delivery	Spontaneous	Spontaneous	Low forceps	Emergency Caesarean section	Low forceps	Low forceps
Gestation (weeks)	40	36	40	38	33	31
Birth weight (g)	2920	2267	3300	3203	1800	1690
Other medical features of probable significance	-	-	-	-	-	-
Other medical features	-	Small stature	VSD impaired at 2 yrs.	R. Hemiparesis; R. IIIrd nerve palsy.	Neonatal jaundice. Febrile fits clumsy gait. Incoordination	Twin
Home background	Average	Poor	Poor	Good	Poor	Average

TABLE V.10 (continued)

Perinatal features of probable aetiological significance and other medical features in 46 out of 169 ESN/M children.					
Case No.	Neonatal cyanosis N=11				
	135	138	145	152	166
Sex	M	F	F	M	F
IQ	74	68	59	71	62
Mode of delivery	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Gestation (weeks)	40	40	40	39	36
Birth weight (g)	3827	3830	3200	3960	2680
Other medical features of probable significance	-	-	-	-	-
Other medical features	Threatened abortion at 12 weeks.	-	-	Head injury at 12 months	-
Home background	Average	Average	Average	Poor	Poor

Fetal distress

a. The fetal distress noted in 10 cases was recorded by the obstetrician in charge. In all 10 cases it led to intervention - high forceps delivery in 9 cases, Caesarean section in 1 case.

Blue and limp at birth

b. Three of the 4 children recorded as blue and limp at birth, were born in general practitioner units and were transferred to the main hospital for special care - as was the fourth child, who was born at home.

Low Apgar scores

c. Three of the 16 children with low Apgar scores had significant prenatal features - two with chromosome abnormalities, 47,XXY [40] and 46 XX del(15)[107] and one boy [55] with hydrocephalus. Another child [139] had prolonged apnoea when 3 weeks old.

Another 3 children had assisted breech delivery - [11, 94, 107].

Four were delivered by Caesarean section - 2 [90,156] were elective operations, and 2 [82,109] emergency. In case [82], a second twin, the cord had prolapsed: in case [109] labour had failed to progress after induction for toxæmia.

Two other children, [31,101] with Apgar scores of 4 at 5 minutes, had the cord around the neck at birth.

Neonatal twitching

d. This had been noted in 5 children. One was the child [115] with congenital adrenal hyperplasia, another [151] was subsequently diagnosed as hydrocephalic.

Fits occurred in the first few weeks of life in 1 girl [118] but had not occurred since. Another child [48] with neonatal twitching

developed grand mal epilepsy aged 3 years and had several major fits over the next 3 years. He was still on phenytoin when seen.

Neonatal cyanotic episodes

e. Eleven children had had episodes of cyanosis or apnoea during the first week of life. Two of these [41, 125] were born at 33 and 31 weeks gestation respectively. One child [23] had a Caesarean section for an unstable lie. At the age of 1 year he was noted to have a right hemiparesis and a third nerve palsy.

The other 8 children had normal deliveries at term and no gross neurological deficit.

Sex

f. There were 30 males with major perinatal features, and 16 females. This, however, was not a significant sex difference.

(χ^2 table 1.58: 1 DF=1 >0.10)

Comparison of major perinatal features
in study children and their normal siblings

One hundred and thirty nine study children had no prenatal or postnatal feature likely to be associated with their retardation. Of these, 120 had 1 or more siblings attending normal schools. (*The sibling nearest in age to the study child was used as a paired control for perinatal events of probable significance.*)

The sex of study children and their paired controls is shown in Table V.11.

TABLE V.11

Sex of study children and paired sibling controls used to compare major perinatal events.

Study child	Control child	No
Male	- Male	48
Female	- Female	43
Male	- Female	16
Female	- Male	13
Total		120

Perinatal events in the two groups are shown in Table V.12.

TABLE V.12

Perinatal features in 120 mildly mentally retarded children and paired siblings receiving normal education who acted as controls.

	No of study children	No of control children	
No adverse features	87	111	
Adverse features	33	9	
Fetal distress		9	3
Apgar score <7 at 5 minutes		11	5
Blue and limp at birth		2	1
Twitching or cyanosis during first week		11	0

Recordings of fetal distress or low Apgar scores were less than half as common in the control group as in the study group.

No child in the control group had recorded neonatal twitching or cyanosis.

Overall, the incidence of adverse perinatal factors was significantly less in the control group.

$$(x^2 = 16.6 : DF=1 : p<0.001.)$$

COMMENTS

Association between mental retardation and perinatal stress.

The extent of any relationship between birth trauma and subsequent mental retardation is well nigh impossible to determine. Attempts at assessing any link are fraught with problems. One is that children with apparently similar degrees of trauma may be severely retarded, mildly retarded, or have no apparent after effects with normal intelligence. This is in contrast to, say, Down syndrome where all affected children will have some limitation of intelligence, albeit this may range from severe retardation to the upper limits of mild retardation.

Recent studies have failed to resolve the degree of association, although *Nelson and Ellenburg (1986)* suggest that not more than 10% of neurological handicap in surviving infants is due to perinatal asphyxia.

Prevalence of perinatal stress in mild mental retardation

There is no general agreement as to criteria for a diagnosis of perinatal asphyxia, and estimates of incidents vary from 2.9 to 9 per 1000 births per general population (*Agustsson, 1988*). Studies by *Hagberg (1981)* and *Czeizel (1980)* found perinatal stress in 18% and 16%, respectively, in children with MMR (Table V.13). In another similar study by *Blomquist (1981)*, however, the incidence was lower - 7%, comparable to that found in our control group. *Gillberg (1990)* showed an increased prevalence of neonatal risk factors, including reduced Apgar score and respiratory stress, in a group of 83 Swedish schoolchildren with MMR. Conversely, however, many children with MMR have no history of perinatal insult.

Pre-existing factors

A fetus who is already compromised at birth is more likely to react adversely to intrapartum stress (Nelson, 1986). Five of the children in this study had known prenatal features which would have influenced perinatal events. Levene (1985), in a Leicester study found intra-uterine growth retardation (IUGR) in 25% of infants with perinatal asphyxia. None of the children with perinatal stress in this study had IUGR; three with low birth weights were premature. However, one cannot rule out the possibility that an adverse reaction to perinatal stress is the result of a fetal constitutional defect.

Hypoxic ischaemic encephalopathy

Perinatal insults may not, of themselves, be significant in the absence of hypoxic ischaemic encephalopathy (Robertson, 1989). However, records of this group of schoolchildren born prior to such a concept, were inadequate to assess, with even reasonable accuracy, the extent of any hypoxic ischaemic encephalopathy. Symptoms of mild hypoxic ischaemic encephalopathy, such as hyperalertness or difficulty in feeding, would not necessarily be recorded. Consideration has therefore been limited to features accepted as signs of perinatal stress.

Motor disability

It has been suggested (Gillberg, 1990) that mental retardation not accompanied by motor impairment is only rarely associated with perinatal asphyxia. This study showed the prevalence of incoordination to be increased, but mildly so, in children with a history of perinatal stress. However, any brain damage in mild mental retardation is, by definition, mild. Minor damage to higher cortical centres could, conceivably, occur independently of motor damage.

Diagnosis of perinatal stress

Another problem in considering results of the present study is that in 1971-1976, when the survey children were born, there were no facilities for detailed fetal or neonatal monitoring; assessment was based on subjective clinical impression. However, children in whom a diagnosis of perinatal stress was based on mention of "fetal distress" or "blue and limp" in the case notes have been included in this group only when such observations led to altered management.

Apgar scores, when used, are rather more specific but again, the association of reduced Apgar scores with neurological deficit is variable (*Nelson, 1981.*)

Neonatal apnoea or cyanotic attacks probably indicate asphyxia (*Brown, 1974.*) and have therefore been included as risk factors.

Environmental factors

Another problem is the gap of several years between birth and the children being seen at school. Severe mental retardation possibly arising from birth trauma will be evident at an early stage in life and the probable association recognised. Milder brain damage possibly due to birth injury may not become evident for several years, especially when motor development is unimpaired.

Galbraith (1978) looked at 42 infants aged 1 year, with a history of perinatal asphyxia. Their mental and physical development did not differ from a group of 69 control infants. It may only be when the child fails to respond to the demands of school work, that any intellectual deficit becomes apparent. In the intervening years, environmental factors, medical and social, will influence the child's development, and may augment - or reduce - any sequelae of perinatal brain ischaemia. With the passage of time, any association will become blurred.

However, even with such limitations - of diagnosis of perinatal stress, of knowledge of long-term effects of perinatal stress and of environmental factors modifying the eventual outcome - perinatal stress cannot be disregarded.

Control population

In assessing possible aetiological aspects of perinatal stress, it was felt that a control population would be of value.

Siblings were used for the control group to mitigate familial and social influences as much as possible. This had the disadvantage that controls were not available for all children, as some study children had no siblings of school age attending normal schools.

Neither were controls specifically matched for sex as this would have reduced numbers further. However, 91 out of 120 controls were in fact of the same sex, and in the other 29 children, the male-female and the female-male discrepancy was almost balanced. (Table V.12)

Prevalence of perinatal stress in the study and control populations

The risk factors used - fetal distress, Apgar scores <7, blue/limp at birth and twitching or cyanosis in the first week of life - had occurred in 46 (27%) of the 169 ESN/M children. Five of these children had major aetiological prenatal features. Excluding them, perinatal stress had been recorded in 41 (24%) study children. In their normal sibling controls the prevalence of perinatal stress was 7%. Even allowing for the many variable factors considered above, this positive association suggests that perinatal stress has a significant aetiological role in mental retardation.

A possible relationship between incoordination and perinatal stress is discussed in Section VII. 6.

SECTION V - MEDICAL FEATURES OF PROBABLE AETIOLOGICAL SIGNIFICANCE

C. POSTNATAL EVENTS

Post natal events were considered significant if the child had been developing normally before the event, but showed developmental delay thereafter.

Results

Such events were identified in 8 children (4.7%). (Table V.14)

The 3 children [1, 79, 164] with infections of the central nervous system (CNS), the 2 children with apnoea [117, 139] and the child [124] with prolonged status epilepticus, all had marked behaviour problems, with inappropriate or unpredictable responses. There was felt to have been gradual improvement in all 3 children with early CNS infections, but the child with prolonged apnoea at 6 weeks was deteriorating. His IQ at ESN/M school entry aged 8 years, was 77: when retested, shortly before being seen, at the age of 11 years, it was 54 and transfer to an ESN/S school was being considered.

The child [49] with residual hemiparesis and visual problems following traumatic subdural haematoma, had features of Sotos syndrome. She was large at birth - over 10 lbs. had a long, narrow mandible and high forehead, was tall and had large hands and feet. She did not however, have a large head - her OFC was 2 centiles below that of her height. Her bone age had not been recorded. It was felt that a diagnosis of Sotos syndrome was not justified.

The child [14] with severe pertussis had physical and mental delay after the infection, with a retarded bone age. His IQ was 83; he had no behaviour problems.

TABLE V.14

Postnatal events of probable aetiological significance in
8 out of 169 ESN/M children.

Case No.	1	79	164	117
Event	Haemophilus meningitis	Meningitis	Encephalitis	Prolonged apnoea
Sex	M	F	F	M
IQ	66	70	80	71
Age of occurrence	9 weeks	6 weeks	3 years	6 months
Remarks	Bilateral subdural effusion. Grand mal epilepsy till 18 months old. Aggressive behaviour until 4 yrs old-still antisocial.	Macular rash, febrile signs of CNS irritation. CSF and blood-no growth. At same time - swelling of L. internal Malleolus subsided spontaneously. Antisocial behaviour	No virus isolated. Has since had grand mal fits about 1 per month; on sodium valproate. Behaviour very disruptive, gradually improving.	Found cold and limp in pram. Resuscitated by father in ? 5 mins. Behaviour unpredictable, speech delayed-articulation defect.
Other medical features	-	-	-	-
Home background	Good	Average	Average	Average

TABLE V.14 (continued)

Postnatal events of probable aetiological significance in 8 out of 169 ESN/M children.				
Case No.	139	124	49	14
Event	Prolonged apnoea	Status epilepticus	Intracranial haemorrhage	Severe pertussis
Sex	M	M	F	M
IQ	52	59	60	83
Age of occurrence	3 weeks	14 months	16 months	2 years
Remarks	Found blue and limp in cot. Resuscitated by father in 20 mins Mild hypotonia thereafter. Speech very limited. Grand mal fit aged 8 yrs. On carbamazepine. Lack of short term memory. Disorientated behaviour. EEG - paroxysmal disturbance. CT scan - normal IQ reduced over last 4 yrs.	Febrile convulsions developed into status epilepticus- took 3-4 days to be controlled with phenobarb- itone. Petit mal thereafter till 6 yrs old, EEG normal. Inappropriate behaviour. Perceptual problems. Poor coordination.	Non-accidental head injury: followed by fits and bilateral subdural haematomata, released 6 wks after the injury. Persistent L. sided weakness. Poor visual coordination. Perceptual problems.	Very ill for 3 months, took 1 year to recover. Developmental delay thereafter. Retarded bone age at 3 and 4 yrs. Small stature Incoordination.
Other medical features	-	Placental insufficiency. Birth weight on 25th centile. Treated neonatal jaundice.	Features of Sotos syndrome.	Threatened abortion-at 6 and 10 wks gestation.
Home background	Good	Good	Average	Good

COMMENTS

a. Postnatal events formed a relatively small proportion (11%) of the probable medical aetiological factors identified in the survey.

b. None of the children in this group came from 'poor' social backgrounds. There was nothing to suggest that children in the lower social strata are at increased risk of postnatal infection or trauma liable to cause brain damage.

c. Abnormal behaviour patterns were a prominent feature in all 6 children who had CNS infections, prolonged apnoea or status epilepticus between the ages of 6 weeks and 3 years. The 3 children with CNS infections, and the boy who was apnoeic for 5 minutes, were aggressive children, difficult to control; abnormal behaviour patterns in the child with prolonged status epilepticus, and in the child who was apnoeic for 20 minutes, amounted to psychoses.

Behaviour was normal in the child who had severe pertussis, and in the girl with subdural haematomata released two months after a head injury. The brain insult in these 2 children may have been less acute.

d. It was of interest to find the child in whom severe pertussis at the age of 2 years appeared to have resulted in mental and physical delay. A survey, by a group of general practitioners *Swansea (1987)* of a group of 27 children who had had severe pertussis under the age of 5 years, found their median IQ and school attainment 7 years later to be significantly lower than those of 27 children who had not had pertussis and of 15 children who had had mild pertussis.

SUMMARY OF FINDINGS IN SECTION V

MEDICAL FEATURES OF PROBABLE AETIOLOGICAL SIGNIFICANCE

1. Medical features which had probably contributed to the ESN/M school referral were identified in 71 (42%) study children -(Table V.15)

TABLE V.15

Medical features of probable aetiological significance in 71
out of 169 study children.

	No. (%)
Prenatal	22 (13)
Perinatal	46* (27.2)
Postnatal	8 (4.7)

* includes 5 children with major prenatal features.

2. Fourteen children had features of genetic origin. Two children had syndromes of Mendelian inheritance, but neither was diagnosed before the age of 7 years. Genetic syndromes in 3 other children, and 8 chromosome abnormalities, were all of sporadic occurrence. It is unlikely that genetic counselling would have any significant effect in reducing the prevalence of MMR in the local community, especially as -

3. Contrary to expectation, no cases of fragile-X were identified and - perhaps less surprisingly -

4. No inborn errors of metabolism were found during the survey in mothers or children.

5. Chromosome analysis, and a careful examination for possible genetic syndromes are recommended as routine investigations for all children referred to ESN(M) schools.

6. A diagnosis was made in 11 survey children (3 genetic syndromes, 6 chromosome abnormalities, 2 environmental fetopathy). A firm diagnosis can be of value to parents and to those involved in the child's management, by helping to provide a prognosis and, if relevant, a basis for treatment.

7. Alcohol fetopathy was not a major contributory factor - only 1 case of FAS was found.

8. Perinatal stress had occurred in 46 children, 5 of whom also had prenatal features.

The incidence of perinatal stress in study children was significantly increased over that of a sibling control group. Evidence from this study suggests a significant link between perinatal stress and MMR.

9. Postnatal features occurred in 8 children, all from good home backgrounds.

Features in the preceding section - Section V - have a recognised link with mental retardation.

There were two other groups of medical features noted in the children -

1. Abnormal medical features occurring in the prenatal, perinatal, or postnatal periods, which have no established link with mental retardation.

- *Section VI*

2. Abnormal medical features of uncertain origin, which have no established link with mental retardation, but which may indicate significant underlying pathology.

- *Section VII*

SECTION VI- PRE-, PERI-, AND POST-NATAL MEDICAL FEATURES OF
POSSIBLE AETIOLOGICAL SIGNIFICANCE

Less than half the mothers of study children had had a completely normal pregnancy and labour. Environmental adverse factors of likely association with mental retardation have already been discussed - 3 mothers had major prenatal environmental events and 46 had major perinatal adverse histories; 8 children had postnatal medical risk factors.

Minor pathological features occurring during pregnancy or labour had affected a further 40 mothers. Overall, 89 (57%) had some adverse feature during the pregnancy or labour with the study child. Minor postnatal events had occurred in 5 children, all of whom had other medical features.

There was some overlap between the occurrences of 'major' - *Section V* - and 'minor' - *Section VI* - factors, and between pre-, peri-, and post-natal features.

In presenting results, I have detailed for each feature considered whether it occurred alone, with a 'major' feature, or with other 'minor' features.

SECTION VI - MEDICAL FEATURES OF POSSIBLE AETIOLOGICAL SIGNIFICANCE

A. PRENATAL FEATURES

Results

Mothers of 56 study children had had minor abnormal events in the relevant pregnancy, and 15 children had features at birth indicating a disruption of normal fetal development - major malformations, very low birth weight. Mothers of 5 of these latter children had not had normal pregnancies : hence, overall, abnormal prenatal features of possible significance were identified in 66 children.

Table VI.1 lists the overall occurrence of these features, and their association with other known/possible risk factors. Further details are given in the text.

TABLE VI.1

Prenatal features with no well established link with mental retardation
in 66 out of 169 mildly retarded children.

Feature	No. of children with each feature (N = 66)	No. of children in whom this was sole medical feature (N = 13)	No. of children with a known risk factor. (N = 36)	No. of children with one or more other features. (N = 34)	
				One	More than one
Twining	9	0	2	2	5
Chromosome translocation	1	0	0	0	1
Maternal diabetes	3	3	0	0	0
Maternal medication	6	0	2	2	2
Maternal operation	1	0	0	0	1
Maternal injury	2	1	0	1	0
Threatened abortion	8	1	4	2	1
Hyperemesis	14	2	7	3	2
Maternal toxaemia	14	4	9	0	1
Maternal anaemia	5	0	1	0	4
Small for gestational age	11	1	5	2	3
Birth weight <2000gm	5	0	4	1	0
Major malformation	4	1	2	0	1

a. Twinning

Of the 9 twins in the survey, 1 pair [19,20] were small-for-dates. No other adverse features were identified in these 2 girls. Seven other twins were born prematurely.

The mother of another pair of twins [27,28] had received parenteral iron for anaemia in pregnancy.

One male twin [125], who had neonatal apnoea, had a twin sister attending a normal school.

b. Chromosomal translocations

Although minor dysmorphic features found in the study children are discussed later, it seems appropriate to mention here that the boy [59] with an apparently balanced familial translocation has been included in this group because he had distinctive dysmorphic features.

c. Maternal diabetes

Mothers of 3 children had diabetes mellitus. Two [96,157] had been diagnosed in childhood and were reasonably well controlled with insulin. The third mother [61] was grossly obese, had been diagnosed at the age of 31 years, 3 years before the birth of the study child. Her management of diet and insulin control was erratic, with frequent hyperglycaemic episodes. In all 3 children, maternal diabetes was the sole medical factor found. One child [96] weighed 4770 gms. at birth - well over the 97th centile - but had no problems at delivery; the other 2 children had birth weights within normal limits.

d. Maternal medication

Debendox had been taken for control of hyperemesis by 3 mothers - by 2 [15.152] throughout the pregnancy, and by 1 [150] from the 3rd-7th months. This was the sole medical feature in case [15].

Oral contraception - Ovran in both cases - had been continued into the pregnancy by 2 mothers - for the first 3 months [97] and the first 4 months [42]. In neither mother was this the sole medical feature.

One mother [83] took phenytoin and phenobarbitone for control of epilepsy. She had no major fits when pregnant. The child had no dysmorphic features - in particular, none of the dysmorphic features of fetal hydantoin syndrome.

e. Maternal operation

An appendectomy was carried out on mother [169] when she was 16 weeks' pregnant, and was followed by a troublesome wound infection. She also had severe hyperemesis throughout pregnancy, and toxæmia with ankle oedema and raised blood pressure.

f. Maternal injury

One mother [66] was involved in a car accident when 18 weeks' pregnant. She received a blow to her abdomen, was shocked and admitted to hospital for 2 days, but had no vaginal bleeding or skeletal injury. There were no other medical features identified.

Another mother [130] fell downstairs at 32 weeks' gestation. She had a slight 'show' thereafter, and diminished fetal movement. At delivery, 8 weeks later, she was found to have ruptured membranes. This, again, was the sole medical feature noted.

g. Threatened abortion

Vaginal bleeding in the 1st or 2nd trimester of pregnancy had occurred in 8 mothers. (4.7%) In 5 this was a single episode - at 6 weeks' [160], 12 weeks' [134], 15 weeks' [121] and 24 weeks' gestation.[71, 99] In 3 of the mothers there had been repeated blood loss - at 12-16 weeks' [147], 8-16 weeks' [143] and throughout the pregnancy [79]. None of these pregnancies were associated with fetal abnormality or intrauterine growth retardation. In 1 case [160] threatened abortion at 6 weeks' gestation was the only medical feature.

h. Hyperemesis

Early morning sickness in the first few weeks of pregnancy has not been included in this group - only the mothers whose hyperemesis persisted more or less throughout the pregnancy were included. Fourteen mothers were affected.

Three mothers [15, 150, 152] had taken Debendox. In 2 mothers [33,65] hyperemesis was the only medical feature identified.

Seven children had major medical features - Down syndrome [111], encephalitis aged 3 years [164] and perinatal stress in 5 [31, 75, 144, 150, 152]

One mother had a threatened abortion at 15 weeks' gestation, and 1 an appendectomy at 16 weeks' gestation, and toxæmia.

i. Maternal toxæmia

Only those mothers whose rise in blood pressure and/or oedema was sufficient to merit hospitalisation, or early induction of labour, have been included. There were 14 mothers affected. In 4 [8, 131,

142, 161] there were no other medical features. One mother [143] had a threatened abortion, another [169] an appendectomy at 16 weeks' and hyperemesis, and another [42] had taken oral contraception for the first 4 months of pregnancy. Eight had medical features of aetiological significance. Five [40, 78, 107, 109, 143] also had chromosomal abnormalities. One child [104] had Cohen syndrome, one [134] was microcephalic, and the last child [124] in this group had status epilepticus at 14 months of age.

None of these mothers had full-blown eclampsia. The age range was 19-39 years, with an average of 28.2 years at birth of the child. This is only slightly higher than the average maternal age for study children - 25.9 years. (*Section VIII, 4*).

Eight of the mothers were primagravida : another 3 [40, 107, 161] were aged 38 years or over. Only one child [134] born to a mother in this group was small-for-dates at birth.

j. Maternal anaemia

This group included mothers who had received parenteral iron for treatment of anaemia. In none of the children born to such mothers was anaemia in pregnancy the only medical factor noted. The group included 1 pair of twins [27, 28], a child [16] who was small-for-dates, and a child [58] with Prader-Willi syndrome who was also small-for-dates.

k. Small for gestational age

There were 11 children in this group, whose birth weight was on or below the 3rd centile for gestational age.

One child [55] had no other medical features. In another child [25] short stature when seen was the only other medical feature. The

mother of another child [16] in this group, who also had small stature, had been anaemic.

Twins [19, 20] have already been mentioned.

Two children in this group had cleft lip and palate. One [102] was born at 36 weeks' gestation ; the other [43] had fetal distress.

The child [98] with FAS had a very low birth weight - 1980 gms. at 38 weeks' gestation.

Another child [134] with microcephaly, weighed 2130 gms. at 42 weeks' gestation; her mother had hypertension throughout the pregnancy.

The child [58] with Prader-Willi syndrome was born to an anaemic mother.

The last child [94] in this group was born to a 41 year old mother. There were no problems in pregnancy, but the child did have a low Apgar score at birth.

1. Low birth weight

Five children in the survey had birth weights of between 1600 and 2000 gms, but in none was this the sole medical feature noted.

Two of these - a child [102] with cleft lip and palate, and the girl [98] with FAS, have already been mentioned. They were both below the 3rd centile for gestational weight.

Three other children weighed <2000 gms. at birth but were not small for gestational age.

Two [82, 125] belonged to twin sibships and were born at 31 and 33 weeks' gestation. The third child [41] was born at 33 weeks' gestation to a toxæmic mother. He had blue turns after birth and hyaline membrane disease.

m. Major malformations

There were 3 study children born with cleft lip and palate.

In 1 child [127] this was the sole medical feature.

Two [43, 102] were also small-for-dates, and 1 [43] also had fetal distress. In addition to his cleft lip and palate, this latter child had Poland's anomaly, shown in the photograph in Appendix A.

The fourth child [9] in this group had perinatal problems. He was later found to have a ventricular septal defect (VSD) repaired at 2 years of age.

COMMENTS

Although none of the conditions in this diverse group of prenatal medical features has any recognised association with mental retardation, it is of interest to note that such features occurred in 66 (39%) study children.

a. Twinning

Nine out of 166 (5.3%) study children were twins. In the years 1970-1974, when study children were born, an average of 10 out of 1000 children born were twins. (HMSO, 1974) : One would therefore expect 1.69 study children to be twins. Nine represented a considerable excess. *Blomquist (1981)* also found an excess of twins in a survey of 171 ESN(M) children - 3.5%, compared with an overall Swedish prevalence of 1.25%.

It has been well recognised that twins are more common than would be expected in mental defectives (*Berg, 1960; Husen, 1960.*). In 1970, *Record* found the average IQ of 2146 twins to be 95.7, compared to 100.1 in 50 singletons. The excess of twins in the study was therefore not unexpected.

About 20-30% of twin pregnancies end prematurely, (*Geirsson, 1988.*) with increased perinatal risk. Seven of 9 study twins had been born prematurely: 2 of them had perinatal stress. The other pair of twins, born at 39 weeks' gestation, were of low birth weight. It may be that secondary effects of twinning - premature delivery, competition for maternal resources, contribute to the excess of twins found in retarded populations.

Four sets of twins were identical, presumably uniovular, although details of this were not recorded in the case notes. The other twin

had some perinatal anoxia when born at 31 weeks' gestation. His twin sister had no recorded birth trauma and attended normal school.

In all 4 sets of identical twins, the second twin had a lower IQ than the first. However, this difference in IQ did not exceed 9 points - in keeping with a study by *Newman (1937)* - except for a pair of twins where the second twin had a low Apgar score and an IQ of 16 points less than that of the first twin, who had no perinatal problems.

b. Chromosomal translocations

Case [59] had an apparently balanced translocation between chromosomes 3 and 15. His mother and maternal grandmother carried the same translocation. One might assume, therefore, that this was an incidental finding. However, it has been noted that mental retardation and dysmorphism occur more frequently than one would expect in carriers of apparently balanced, familial translocations. (*Fryns, 1986*) This study child had pronounced dysmorphic features, and did not look like any of his relatives. Some doubt must remain as to whether there is any link between his chromosome abnormality and his retardation.

c. Maternal diabetes

Children born to diabetic mothers have a risk of congenital malformations of up to 8% (*Day, 1976; Soler, 1976.*) - about twice that of the general population. The risk is greatest in children born to mothers whose diabetes was diagnosed under the age of 20 years.

Two of the mothers in this group were diagnosed in childhood : the third mother, diagnosed aged 31 years, had erratic control of blood

sugar levels. However, none of the 3 study children had any apparent dysmorphology, nor signs of caudal regression. I am unaware of any previous suggestion that children born to diabetic mothers are at an increased risk of mental retardation, but in all 3 study children maternal diabetes was the only medical factor noted. Two children came from good homes, and had parents with no educational problems. The mother of the third child had been slow at school, but had 2 older children - born before she developed diabetes - in mainstream education.

The population prevalence of insulin dependent diabetes mellitus is about 1 in 500 - 3 out of 169 study mothers with diabetes is more than would be expected. This increased prevalence, and the fact that no other medical factors were evident in any of the 3 children, suggests a possible need for further investigation into the intellectual abilities of children born to diabetic mothers.

d. Maternal medication

Almost all mothers in the survey, over the whole social spectrum, reacted to the question - "Were you taking any medicine while pregnant?" - with emphatic denial. The thalidomide incident had made mothers ultra-cautious about any medication in pregnancy - even iron was regarded with suspicion by some mothers. Two mothers who unwittingly had continued oral contraception into the pregnancy - one into the third month, the other into the fourth - did not overtly associate this with their child's retardation, but felt guilty. The 3 mothers who had taken Debendox had done so as they felt any possible deleterious effects of the drug would be less than those of severe hyperemesis. Eleven other mothers who had severe hyperemesis did not take medication.

Any adverse influence on brain development from maternal intake of either Debendox or hormones has not been proved. *Fleming (1981)* looked at the outcome of pregnancy in 22,977 women, 620 of whom had taken Debendox in the first trimester. Of these latter women, 589 out of 620 (95%) had a normal outcome of pregnancy. The rate of fetal abnormality in women who had not taken Debendox was higher - 5.4%. *Goujad (1977)* found no increased rate of fetal abnormality in 815 women who had taken hormones in early pregnancy. However, while neither hormones nor Debendox appeared to be associated with any increase in obvious fetal malformation, one cannot entirely exclude the possibility of more subtle adverse effects on brain development.

e. Maternal injury

It is worth mentioning in relation to case [66] that *Czeizel(1980)* in his review of mentally retarded children in Hungary, cited 2 cases where the mothers had received severe abdominal trauma.

Premature rupture of the membranes had probably occurred in the mother of case [130], when she fell at 32 weeks. However, there was no evidence of fetal infection, and it is debatable whether such an injury would have contributed to the child's mental retardation.

f. Threatened abortion

Bleeding in pregnancy had occurred in 4.7% children. This is a lower incidence than that found in a study by *Ornoy (1976)* of children aged 6-12 years. He found that bleeding in pregnancy had occurred in 12% of 153 normal control children, and in 33% of 110 children with CNS abnormalities with plus/minus psychomotor retardation. Although histories obtained in the present study, 7-11 years after the relevant pregnancies may not have been wholly accurate, Ornoy's

findings raise the possibility of a link between gestational bleeding and subsequent mental retardation; this was the sole medical factor in one study child.

g. Hyperemesis

This had been severe and persistent in 14 mothers, but none of the children had intrauterine growth retardation.. There has been no evidence to link hyperemesis with mental retardation, although this was the sole medical feature noted in 2 children.

h. Maternal toxemia

In 4 children maternal toxemia was the only medical feature identified. *Ounsted (1984)* evaluated children aged 7 years who had been born to mothers with mild or moderate hypertension and found no neurological deficit; but *Salonen (1984)*, studying a group of 136 mentally retarded children and 122 controls aged 9-10 years, found a relative risk of toxemia of 6.1% in mothers of retarded children. None of the mothers in this survey had had severe pre-eclampsia : but toxemia may have a minor aetiological role.

The only child who was small-for-dates born to a toxemic mother, had microcephaly; birthweights of the other 13 ranged from 10th centile to 97th centile.

i. Small for gestational age (SGA)

Studies of children who are SGA have yielded conflicting results. Some have reported an increased risk of disability - including MMR (*Parkinson, 1981; Fitzhardinge 1972.*) Other studies have found no

increased risk (*Vohr, 1983; Nilsen 1984*). Although 11 children in this study were SGA, 5 had major aetiological causes for their retardation - 2 prenatal (FAS, microcephaly) and 3 perinatal stress. In just one child was SGA the only medical factor identified.

While some of the associated 'minor' medical factors might conceivably themselves be associated with intrauterine growth retardation - twinning, maternal anaemia, maternal toxemia, and small stature when seen, there were 3 children who had 'minor' medical factors - prematurity, ante-partum haemorrhage, and excessive weight loss after birth - which could possibly, independently, have contributed to MMR. Thus, in spite of 11 children with SGA, there was little evidence from the study that intrauterine growth retardation - per se - is associated with increased risk of mental retardation.

j. Low birth weight

Alberman (1985) found a degree of neuro-developmental disability in 7.1 % of children whose birth weights were between 1750 and 2000 gm and of 10.5% for those with birth weights between 1500 and 1750 gm. Both study children in the latter group had other evidence of disruption in prenatal development - a girl with FAS, and a boy with cleft lip and palate. The other 3 children, all with birth weight appropriate for gestational age, had perinatal events of probable association with their mental retardation. Thus, there was no evidence from this study that low birth weight per se, might be associated with mental retardation.

k. Major malformations

The incidence of cleft lip and palate is 1 in 750 of the population; it was surprising to find 3 affected children in the study population. Cleft lip and palate have no recognised association with mental retardation. Other studies of MMR (*Czeizel, 1980; Hagberg, 1981; Einfeld, 1984*) make no mention of this deformity, but the finding of 3 cases in our study population does raise the possibility of a link. One child had no other medical features : another had also Poland's anomaly - again, not associated with mental retardation - and the third had fetal distress.

The child with a VSD had a strong family history of retardation - both parents had received ESN/M education. The congenital heart defect is unlikely to be linked to his retardation.

SECTION VI - MEDICAL FEATURES OF POSSIBLE AETIOLOGICAL SIGNIFICANCE

B. PERINATAL FEATURES

Abnormal medical features with no established link with mental retardation, which occurred perinatally are shown in Table VI.2.

FEATURES

a. Gestation equal to or less than 36 weeks.

Premature delivery had occurred with 21 children, but in none was this the sole feature identified. Eleven children had significant risk factors associated. One [40] had Klinefelter syndrome: he and another 9 children [3, 41, 52, 82, 101, 118, 125, 166] had major perinatal symptoms; one other boy had Sotos syndrome. Seven of the 9 twins in the survey had been born prematurely, as had one child [102] with a cleft lip and palate; this latter child was the only child in this group who was small-for-dates. The mother of one child [18] had had an antepartum haemorrhage two days prior to spontaneous delivery at 33 weeks' gestation.

Six of these children developed neonatal jaundice of sufficient degree to require phototherapy.

TABLE VI.2

Perinatal features with no well established link with mental retardation
in 32 out of 169 retarded children

Feature	No. of children with each feature (N = 32)	No. of children in whom this was the sole medical feature (N = 2)	No. of children with a known risk factor (N = 19)	No. of children with one or more other features (N = 17)	
				One	More than one
Gestation <36 weeks	21	0	11	2	8
Antepartum bleeding	4	1	0	1	2
Rapid delivery	3	1	1	0	1
Neonatal jaundice	10	0	7	0	3
Excessive weight loss	1	0	0	0	1

b. Antepartum haemorrhage

Four mothers had bleeding prior to labour. All were subsequently delivered per vaginam, of babies in good condition. In one child [84] this was the sole medical factor noted. The child [18] who was born prematurely, is mentioned above. Another child [71] had no other pre- or peri-natal features, but had a severe reaction with prolonged fits to a second immunisation at the age of 1 year. The mother of the fourth child [99] in this group had bled at 28 weeks, but delivered normally at 39 weeks. The child had minor dysmorphic features and small stature.

c. Rapid delivery

One child [86] who had a precipitate delivery was born at home, but was in good condition on arrival at hospital. She had no other medical features. The child [104] with Cohen syndrome had a rapid delivery in hospital. She had an Apgar score of 10 at 5 minutes. The third child [69] was born in hospital to a mother who had severe anaemia, his Apgar score at 5 minutes was 9. He later developed petit mal and behavioural problems.

d. Neonatal jaundice

Ten children had neonatal jaundice requiring treatment. They all had other medical features - 7 [7, 41, 68, 29, 153, 155, 154] with significant aetiological features, 3 [60,113,114] with at least 2 other medical factors.

Jaundice was associated with prematurity in 6 children, but this combination did not occur without other medical features in any children.

e. Excessive weight loss

One child [16] had excessive weight loss following delivery. He was born at 38 weeks' gestation, to a mother who had been severely anaemic in pregnancy. His birth weight was 2290 gms. - well below the 3rd centile. Following a marked fall in weight he was in special care for 2 weeks, and was slow to regain his birth weight. His height when seen was below the 3rd centile.

ASSISTED DELIVERY

Delivery by forceps, or Caesarean section has not been considered as a possible independent adverse factor. Such an event would have happened under supervision and fetal distress would be unlikely to have occurred unnoticed. On the other hand, events such as antepartum haemorrhage, or precipitate delivery, could have led to unobserved perinatal stress.

Thirty-four children (20%) had been delivered by forceps; 8 had recorded fetal stress, and 2 low Apgar scores on delivery.

Ten children (6%) were delivered by Caesarean section. Five were elective operations, done because of previous sections (3) or known placenta praevia (2). One of the children had a low Apgar score at birth; the others had no recorded adverse effects. Five other children had emergency Caesarean sections performed because of delay in labour or recorded fetal stress. Four of these children had low Apgar scores at delivery. The fifth had apnoeic spells postnatally and residual cerebral palsy, with mild spasticity in both legs.

COMMENTS

Of 32 study children with abnormal 'minor' perinatal events, 19 had medical factors of probable aetiological significance.

a. Gestation equal to or less than 37 weeks

This was the most frequent of the 'minor' perinatal factors, but it was not a feature which occurred alone. There were 8 children who had accompanying 'minor' features which could have a possible cumulative effect. Premature delivery per se is unlikely to contribute to mental retardation but might do so by the recognised association with other possible causes, such as twinning, neonatal jaundice.

b. Antepartum haemorrhage

Antepartum haemorrhage has been linked not only to cerebral palsy but also to mental retardation. (Taylor, 1985) In a Dundee study antepartum haemorrhage had occurred in the pregnancies of 12% mothers of 300 children with mental retardation, in 3% of 600 controls. In this study 4 (2.4%) pregnancies had been affected and in only 1 child was antepartum haemorrhage the only medical factor noted. Numbers in this study were relatively small, but antepartum haemorrhage had not occurred as frequently as might have been expected from the Dundee study.

c. Rapid delivery

Although 3 children had had a precipitate delivery, the condition at birth of the 2 children born in hospital, and the one born at home,

gave no cause for concern, and their rapid delivery must have a very tentative link with retardation.

d. Neonatal jaundice

Although it is accepted that severe neonatal jaundice may cause widespread brain damage, and lead to mental retardation, none of the study children had the severe form requiring exchange transfusion. All those included did however, require treatment with phototherapy. Although there has been no satisfactory correlation between a single raised bilirubin level and subsequent impaired intellectual performance (Lucey, 1982); neonatal jaundice must remain a 'possible' contributory cause. It is again worth noting that in no children did it occur alone.

e. Excessive weight loss

The excessive weight loss noted after birth in a child who weighed just 2290 gms. at 38 weeks' gestation, may have enhanced any adverse effect on development of the pre-existing intrauterine growth retardation.

SECTION V - MEDICAL FEATURES OF POSSIBLE AETIOLOGICAL SIGNIFICANCE

C. POSTNATAL FEATURES

Postnatal features with a possible, but not accepted link with mental retardation had occurred in 5 children (Table VI.3). None of these children showed incoordination or behaviour problems.

a. Severe malnutrition

One pair of twins [81, 82] were admitted to hospital with severe malnutrition when 8 months old. They were born at 33 weeks' gestation, with birth weights on the 50th [81] and 10th [82] centiles. One [82] had an Apgar score of 6 at 5 minutes. When admitted they weighed 5030 gms. [81] and 3940 gms. [82] - just over, and just under, half the standard weights for babies of 8 months.

b. Immunisation reaction

One child [71] had a severe reaction, with fits, to a second immunisation at the age of 6 months. His mother had had bleeding at 24 weeks', and again at 32 weeks. Delivery, at 38 weeks', was uncomplicated.

c. Head injury

Head injury, with no evident long term neurological sequelae, had occurred in 2 children. One child [152] born to a mother who had taken Debendox for hyperemesis, had a fractured occiput at 18 months. He was blind for several days thereafter. The other child [113], a premature twin with neonatal jaundice, had two grand mal seizures after a fall at the age of 15 months.

TABLE VI.3

Postnatal features with no well established link with mental retardation in 5 out 169 mildly retarded children					
Feature	No. of children with each feature (N = 5)	No. of children in whom this was the sole medical feature (N = 0)	No. of children with a known risk factor (N = 1)	No. of children with one or more other features (N = 4)	
				One	More than one
Severe malnutrition	2	0	1	0	1
Immunisation reaction	1	0	0	0	1
Head injury	2	0	0	0	2

COMMENTS

It is now generally accepted that transient infantile fits following immunisation are not associated with subsequent brain damage. *Baraff (1988)* looked at a group of sixteen 6-7 year olds who had post-immunisation fits or hypotonia; their IQs did not differ from those of their peers.

There was no outward evidence of neurological damage or of behaviour disorder in any of these children with postnatal 'minor' events.

In all 5 there was a history of familial retardation, and it is doubtful if these postnatal events had contributed to the ESN/M referral.

SUMMARY OF FINDINGS IN SECTION VI

Medical features of possible aetiological significance

1. Medical features which had possibly contributed to ESN/M referral were identified in 76 children. (Table VI.4)

TABLE VI.4

Medical features of possible aetiological significance in
76 out of 169 study children.

	No. (%)
Prenatal	66 (39)
Perinatal	32 (19)*
Postnatal	5 (3)#

* includes 22 children with minor pre/postnatal features.

all 5 children also had minor pre/perinatal features.

2. In 41 of these 76 children a major aetiological medical factor was present; of the remaining 35, 20 had 2 or more minor features.

3. Three children born to diabetic mothers had no other medical factors identified.

4. Four children born to toxæmic mothers had no other medical factors identified.

5. There was an excess of twins (5.3%) in study children.

6. Toxaemia had occurred in 8.2% mothers, as also had severe hyperemesis.

7. Eleven (6.5%) children had birth weights on or below the 3rd centile for gestational age, but this was the sole medical factor in just one child.

8. Twenty-one (12.4%) were born before 37 weeks' gestation, but in none was this the sole medical factor.

9. Apart from maternal diabetes and toxaemia, none of the features considered in this section appeared as possible causes per se of mild mental retardation.

SECTION VII - MEDICAL FEATURES OF UNCERTAIN ORIGIN

This section considers medical findings in the study children which suggest underlying pathology of indeterminate cause which could be linked to mental retardation. Such findings could not be firmly ascribed to a pre- peri- or postnatal cause, and some, e.g. short stature, macrocephaly, could have an environmental or genetic aetiology. Nor are they themselves, with the possible exception of epilepsy, likely to cause mental retardation; any significance they may have is as outward signs of abnormal development, physical or mental.

Children with features invariably linked with an identified diagnosis have not been included in this section - thus the dysmorphic features found in children with a recognised genetic syndrome or chromosome abnormality have not been included.

Abnormal features of uncertain origin found in study children and considered in this section were -

1. Small stature equal to or less than 3rd centile in height for chronological age.
2. Minor malformations three or more of the features as described in Section IV, A, 3.
3. Large occipito-frontal circumference equal to or more than 97th centile for chronological age.

Increased cranial circumference was kept separate from other minor dysmorphic features - it is a notable finding in overgrowth syndrome associated with mental retardation, and especially the fragile-X

syndrome. It was felt, therefore, that it would be of value to record this feature independently.

Abnormalities of mental/neurological development included were

4. Epilepsy

- children requiring long-term anti-convulsant therapy. *[All study children with epilepsy are discussed below.]*

5. Behaviour disorders

- children who had been referred to a psychiatrist, or whose behaviour was considered abnormal by both parents and school staff.

6. Incoordination

- children who failed 2 or more of the tests of gross and fine motor coordination detailed in *Section IV, 3, B.*

Findings are outlined in **Table VII.1.** Details and a summary of findings for each features are given below.

TABLE VII.1

Medical features of uncertain origin found in 85 out of 169 mildly retarded children.					
Feature	No. of children with each feature (N = 85)	No of children in whom this was the sole medical feature (N = 22)	No. of children with a known risk factor (N = 45)	No. of children with one or more other features (N = 18)	
				One	More than one
Height on or below 3rd centile	30	10	8	4	9
Three or more minor malformations	10	2	3	2	3
Head circumference on or above 97th centile	10	3	4	2	1
Idiopathic epilepsy	9	0	5	2	2
Behaviour problems	21	3	11	2	5
Incoordination	42	5	26	4	7

1. SHORT STATURE

Results are summarised on table VII.2

COMMENT

i. Thirty (18%) of the study children had heights on or below the 3rd centile. From population norms, one would have expected 5 of the 169 children to have short stature. There was thus a 6-fold increase of actual/expected children with short stature. Omitting 14 children with chromosome abnormalities and genetic syndromes (none of whom were short) - the percentage is 19% (30 out of 155). The additional medical features which occurred in 21 are shown in the table, which also has details of those 9 children in whom short stature was the only abnormality found.

ii. Medical features which could be associated with environmentally impaired growth featured in relatively few cases [14, 81, 82, 98.] Three other children [16, 43, 94.] with intrauterine growth retardation had remained small, and their small stature may have had a prenatal origin - although 8 children who were small-for-dates at birth were not excessively small when seen. In 10 children, short stature was the sole medical feature.

iii. Emotional deprivation may impair growth in children. Home circumstances of the study children are discussed in *Section VIII,6* ; 'poor' home circumstances were felt to exist in some relatively affluent homes where there was little parent-child rapport, as well as some socially deprived, problem families. Sixteen children - half of the affected - with short stature came from a 'poor' home background; in this group there were 3 children [82, 98, 120.] with a medical feature which had probably contributed to the retardation. Six [4, 16, 71, 81, 113, 114] with a possible medical aetiology. In 7 of the children there were no other medical features in their history

or examination. In all 16 children the 'poor' home background may have contributed to the impaired physical growth and mental development.

iv. There were, however, 4 short children [13, 64, 85, 146.] with no other medical features, and 6 [25, 28, 83, 99, 169, 104.] with medical features of doubtful significance in whom there was no evident emotional deprivation. In these 10 children, the cause of both the short stature and the mental retardation remains obscure.

v. Irrespective of associated medical or socio-economic factors, the finding of short stature in 18% of these retarded children suggests a positive link between their delayed physical and mental development.

TABLE VII.2

Findings in 30 out of 169 ESN/M children with small stature.						
Case No.	3	4	14	16	25	28
Sex	F	M	M	M	F	F
IQ	69	-	83	74	75	52
Prenatal factors	-	-	Bleeding at 6/52	Anaemia	-	Twin Anaemia
Gestation (weeks)	36	40	40	38	41	36
Birth weight (g)	2267	3345	3912	2290*	2865	2500
Perinatal factor	<u>Cyanotic turns in 1st week</u>	Caesarean section for placenta praevia	-	Excess weight loss	-	-
Postnatal factors	-	-	<u>Severe pertussis aged 2 yrs</u>	-	-	-
Other medical features	-	Autistic behaviour	-	-	Incoordination	-
Home background	Average	Poor	Good	Poor	Good	Average

* - Birth weight equal to or less than 3rd centile for gestational age

TABLE VII.2 (continued)

Findings in 30 out of 169 ESN/M children with small stature.					
Case No.	43	53	71	81	82
Sex	M	M	M	M	M
IQ	-	66	75	74	58
Prenatal factors	Growth retardation	-	Bleeding at 24 and 32 weeks	Twin	Twin
Gestation (weeks)	41	41	38	33	33
Birth weight (g)	2150*	2670	2750	2330	1680
Perinatal factors	<u>Fetal distress</u>	-	-	-	LSCS- <u>Apgar score 6 at 5 mins</u>
Postnatal factors	-	-	Fits following 2nd immunisation	Gross malnutrition in 1st 8/12	Gross malnutrition in 1st 8/12
Other medical features	Cleft lip/palate Poland's anomaly Incoordination	Abnormal behaviour. Incoordination	-	-	-
Home background	Average	Poor	Poor	Very poor	Very poor

* - Birth weight equal to or less than 3rd centile for gestational age

TABLE VII.2 (continued)

Findings in 30 out of 169 ESN/M children with small stature.					
Case No.	83	98	99	113	114
Sex	M	F	F	M	M
IQ	80	70	63	63	58
Prenatal factors	Epileptic mother on phenytoin	Alcohol ++	Bleeding at 28 wks	Twin	Twin
Gestation (weeks)	37	33	39	36	36
Birth weight (g)	2834	1930*	2608	2520	2470
Perinatal factors	Elective LSCS	LSCS for placental praevia	-	Jaundice	Jaundice
Postnatal factors	-	-	-	Head injury at 15 months, followed by 2 grand mal fits	-
Other medical features	-	<u>Fetal alcohol syndrome</u>	Dysmorphic- bird-like face with large nose Asymmetric chest wall	-	-
Home background	Average	Poor	Good	Very poor	Very poor

* - Birth weight equal to or less than 3rd centile for gestational age.

TABLE VII.2 (continued)

Findings in 30 out of 169 ESN/M children with small stature.					
Case No.	120	139	169	103	94
Sex	F	M	M	M	M
IQ	63	52	80	69	61
Prenatal factors	-	-	Appendicectomy at 16 wks. Hyperemesis throughout. Raised blood pressure.	-	-
Gestation (weeks)	41	42	39	34	40
Birth weight (g)	3230	3180	2660	2250	2070*
Perinatal factors	<u>Severe birth asphyxia</u> Hypoglycaemia	-	Forceps for face presentation	-	<u>Apgar score 6 at 5 mins</u>
Postnatal factors	-	<u>Prolonged apnoea at 3 weeks</u>	-	-	-
Other medical features	-	Epilepsy Behaviour disorder	-	-	-
Home background	Poor	Good	Good	Average	Average

* - Birth weight equal to or less than 3rd centile for gestational age.

TABLE VII.2 (continued)

Findings in 30 out of 169 ESN/M children with small stature.				
Children with no other medical features				
Case No.	13	24	37	64
Sex	F	M	F	M
IQ	78	76	72	71
Gestation (weeks)	40	40	40	41
Birth weight (g)	3912	2802	3005	3720
Home background	Average	Poor	Poor	Average

Case No.	73	85	108	112	146
Sex	F	M	F	F	M
IQ	67	72	58	54	71
Gestation (weeks)	40	40	40	38	40
Birth weight (g)	3760	3175	2820	2680	2940
Home background	Poor	Poor	Poor	Very poor	Average

SUMMARY

1. Short stature - found in 30 study children - had a prevalence 6 times that of the general population.
2. Three of these children had intrauterine growth retardation - one of whom had grossly abnormal physical development - and 4 had adverse medical environmental factors which would have inhibited growth.
3. Home circumstances were unfavourable in 16 of the 30 children.
4. In 9 children with favourable home circumstances short stature was unexplained.

2. MINOR DYSMORPHIC FEATURES

Results are shown in **Table VII.3**

COMMENTS

i. These have been described as

" minor anomalies of no serious medical or surgical consequence to the patient, although they may be of cosmetic concern." Smith (1964)

Recognised genetic syndromes associated with mental retardation, whether chromosomal - e.g. Down, Wolf-Hirschorn, or without an identified chromosomal defect - Rubenstein-Taybi, Coffin-Lowry - each have a pattern of specific but minor dysmorphic features. The occurrence together of such minor physical anomalies and mental retardation suggests a disruption in morphogenesis which affects both external and cerebral development. Hence minor physical anomalies in study children could be linked to their mental retardation, even though the abnormal physical features do not conform to a recognised syndrome. *Features noted are given in Section IV, A, 3.*

Minor dysmorphic features are not uncommon - *Marden et al (1964)* found a single minor abnormality in 15% newborn infants, two abnormalities rather less frequently and 3 or more in 1%. *Smith (1964)* looked at a group of 50 children with idiopathic mental retardation, 50 with VSD and 50 with cleft lip/palate. The number of retarded children with 3 or more minor dysmorphic features was more than twice that in the VSD group, and four times that in the facial cleft group. Although the presence of multiple congenital abnormalities in a child with mental retardation does not prove that the defect in brain function is also a congenital abnormality, *Smith* considered that

"the finding of 3 or more congenital abnormalities appears to indicate a significant abnormality in prenatal development."

The presence of 3 or more minor dysmorphic features is widely accepted as being of significance by workers in this field, and study children fulfilling this criterion, and having no recognised genetic syndrome, have been included in this group.

ii. Dysmorphologists agree about the difficulty of verbal descriptions of "odd-looking" individuals. The photographs of the children shown in the appendix provide more information about their appearance than the short summaries in the table.

iii. Four children had medical features of probable significance in their history. One child [49] had features suggestive of Sotos syndrome, but a non-accidental injury at 6 months old resulting in a brain haemorrhage and hemiparesis was probably directly related to her retardation. However, in 3 children [92, 147, 148] with perinatal problems, there could be a possible link with their dysmorphic features. Disruption of morphogenesis - even of a relatively minor nature - in fetal life could have increased their susceptibility to stress factors at birth. It is interesting to note that all 3 of these children had skull and facial asymmetry and minor hand abnormalities.

TABLE VII.3

Findings in 10 out of 169 children with more than 3 minor dysmorphic features.					
Case No.	6	36	49	38	59
Sex	M	M	F	F	M
IQ	86	51	60	67	48
Dysmorphic features	Prominent metopic suture Prominent nasal tip. Prominent antihelix R+L High palate. Asymmetric chest	Brachycephaly synophrys. Narrow jaw. High palate. Large, prominent ears.	Long face, narrow palate Extra crease on digits 1-4, R+L Long hands and feet-?Sotos syndrome.	Down's-like appearance. Mongoloid slope to eyes Depressed nasal bridge Misplaced incisors. Clinodactyly R+L	Long, narrow skull-face. Very high, narrow palate. Telecanthus Very short digits
Prenatal factors	-	-	-	Hyperemesis	46,XYt,(3:15) (familial)
Gestation (weeks)	40	41	40	41	37
Perinatal factors	-	-	-	-	-
Postnatal factors	-	-	<u>Intracranial haemorrhage at 16 months.</u>	-	-
Other medical factors	Macrocephaly Behavioural disturbance	-	Left hemiparesis	-	Epilepsy Behavioural disturbance
Parental retardation	-	-	-	-	-

TABLE VII.3 (continued)

Findings in 10 out of 169 children with more than 3 minor dysmorphic features.					
Case No.	92	99	137	147	148
Sex	M	F	F	M	M
IQ	71	63	73	80	63
Dysmorphic features	Skull and facial asymmetry. Lateral displace- ment inner canthus. Prominent nasal bridge. Bilateral clinodactyly. L.Simian crease.	Bird-like face Prominent nasal bridge, relatively large nose. L.clinodactyly Wide-spaced nipples. Chest asymmetry. OFC - 2SD	Medial eyebrow flare. Small palpebral fissures. L eye lower than R. Epicanthic folds. Long philtrum. Simple ears with thick helical rim.	Skull and facial asymmetry. Short, spatulate digits, Bilateral clinodactyly Small 5th nails. Syndactyly toes 2-3 R+L	Skull and facial asymmetry. Prominent helical rim. High palate. Long digits Mild scoliosis
Prenatal factors	-	Bleeding at 28 weeks	-	Bleeding between 12-16 weeks.	-
Gestation (weeks)	41	39	40	41	37
Perinatal factors	<u>Cyanosis in 1st week</u>	-	Elective LSCS	<u>Fetal distress</u> High forceps delivery	<u>Apgar score 5 at 5 mins</u>
Postnatal factors	-	-	-	-	-
Other medical factors	-	Small stature	-	-	Macrocephaly
Parental retardation	-	-	-	-	-

iv. One child [59] who had a distinctly 'odd' appearance had an apparently balanced chromosome translocation. His mother and maternal grandmother, neither of whom were dysmorphic or retarded, had an apparently similar translocation. Thus any relevance of this chromosome abnormality in the study child is doubtful. Children with de novo apparently balanced chromosome translocations may be at increased risk of mental retardation (*Warburton, 1984*) - this question is the subject of an on-going study in the U.K. - but it is generally assumed that a balanced translocation inherited from a parent will not affect the phenotype. *Fryns (1986)* suggested that although multiple malformations and mental retardation are rare in cases of familial balanced translocations, they are more common than in those with normal karyotypes. However, any link between the balanced translocations and mental retardation in this child must remain dubious.

v. The 5 other children [6, 36, 38, 99, 137.] who had several dysmorphic features, had no significant medical history. In them, the putative link between external physical anomalies and cerebral development must be considered a possible aetiological factor.

vi. Although none of these children had dysmorphic features consistent with a recognised genetic syndrome associated with mental retardation, and hence their odd appearance could not be directly linked to their need for ESN/M education, there remains the possibility of an association between the two - in a study of 199 school age children - aged between 6-7 years, *Rosenberg (1973)* found the number of minor physical abnormalities to be inversely related to verbal performance.

MINOR DYSMORPHIC FEATURES - CONTROL GROUP

1. The identification of minor dysmorphic features, especially those of the face, is highly subjective. Children in the survey had their outer and inner canthal distances measured, but even such limited facial measurements can be subject to observer error. About 20 clinical geneticists at a meeting attended by the author were asked to measure the outer and inner canthal distances of 3 subjects, independently. Results varied widely!

2. It was therefore decided to study a control group of children attending normal schools for dysmorphic features.

These children were not individually paired, but were within the same age range as study children. Details of their recruitment are given in *Section IV, 5*.

- Parents of 60 children were asked for permission to examine their children. One refused.

- Four children, for whom permission for examination had been given, were absent on the day of the school visit.

- 55 control children were examined for dysmorphic features.

ASSESSMENT OF DYSMORPHIC FEATURES

Children with an identified medical aetiological feature were excluded when considering a possible link between retardation and dysmorphic features for 2 reasons -

- a) the recognised cause could itself be linked with dysmorphology - as in chromosome abnormalities and genetic syndromes.
- b) any medical feature probably associated with retardation would prejudice assessment.

Consideration was given below (*Section VIII,3*) to any history of parental retardation in the study children. This familial feature was taken into consideration in assessing dysmorphic features and children were grouped accordingly.

The prevalence of dysmorphic features in control children and in these 2 groups of study children were compared -

- a) study children with no identified medical aetiology, but a history of parental retardation.
- b) study children with no identified medical aetiology and no history of parental retardation.

Results

Numbers of children in each of the 3 groups with no, 1, 2, and 3 or more than 3 minor dysmorphic features are given in **Table VII.4**

TABLE VII.4

Dysmorphic features in 3 groups of children.

	Control	Study/Parental	Study/No Parental	Total
		Retardation	Retardation	
Minor Dysmorphic Features	No. (%)	No. (%)	No. (%)	
0	8 (14)	9 (16)	4 (10)	21
1	19 (35)	20 (35)	4 (10)	44
2	26 (48)	19 (33)	11 (27)	53
3 or more	2 (3)	9 (16)	22 (53)	35
<hr/>				
Total	55	57	41	153
<hr/>				

SUMMARY

a. In this study minor dysmorphic features were found more frequently in the control group than in the study by *Marden (1964)* of 4,412 newborn infants.

36% control children, as opposed to 15% in the Marden study, had 1 dysmorphic feature.

3% control children as opposed to 1% in the Marden study had 3 or more dysmorphic features.

This difference emphasises the subjective element in assessing dysmorphology, and the value of using control children in assessing any significance of dysmorphic feature study children.

b. Of study children with no recognised aetiological feature and no history of parental retardation, 53% as opposed to 3% control children had 3 or more minor dysmorphic features.

This difference is highly significant ($DF = 1: x^2 = 31.3 : p > 0.001$) It is acknowledged that observer bias may have influenced this finding - the examiner knew in advance whether the child had MMR or was a control. However, the difference is so striking that it is highly improbable that any such bias could account for the results, which must therefore be regarded as significant. This increased prevalence of dysmorphic features in these children with no evident aetiology, suggests the possibility of an embryonic insult affecting both physical and cerebral development.

c. There was a significant difference in the prevalence of 3 or more dysmorphic features in study children with no aetiology evident, who did have a history of familial retardation and those who did not : in the latter group the prevalence was 53%, in the former 16%.

($DF = 1 : x^2 = 15.8 : p > 0.001$)

The prevalence of 16% children with 3 or more dysmorphic features in such study children was greater than that of 3% in the control group,

but this difference was not of high significance.

(DF = 1: $\chi^2 = 4.6$: 0.05 > p > 0.02)

3. MACROCEPHALY

Results

- i. This was noted in 11 children (Table VII.5) of whom 10 were male.
- ii. One child [155] was found to have hydrocephalus a few weeks after birth : this was followed up, without surgical intervention. Another child [144] was large overall, with height and weight also >97th centile.
- iii. Four of the children with macrocephaly [124, 144, 148, 155] had medical features in their history which could have contributed to their retardation.
- iv. Of interest were two brothers [88, 89] who, while not having enough minor dysmorphic features to be included in that group, did have broad foreheads with hair growing low over the forehead, and prominent glabellae. Both parents had had problems with education. The study did not include measurements of parents' heads, but there remained the possibility of familial macrocephaly, which is sometimes associated with mental retardation.
- v. One of these brothers was born at 34 weeks' gestation but the other, and 3 further children in this group, had no abnormal medical features in their previous history.

TABLE VII.5

Findings in 11 out of 169 children with macrocephaly.						
Case No.	6	32	34	88	89	124
Sex	M	M	M	M	M	M
IQ	86	70	58	59	53	59
Prenatal features	-	-	-	-	-	Toxaemia
Gestation (weeks)	40	40	40	40	34	37
Birth weight (g)	3685	3061	2806	3720	2012	2863
Perinatal features	-	-	-	-	-	Jaundice
Postnatal features	-	-	Febrile fits at 2-3 yrs	-	-	Status epilepticus at 14 months
Other medical features	>3 Dysmorphic features Behaviour disorder Incoordination	Epilepsy	-	Low hair line	Low hair line	Behaviour problems Incoordination
Parental retardation	-	+	-	+	+	-

TABLE VII.5 (continued)

Findings in 11 out of 169 children with macrocephaly.					
Case No.	144	148	155	158	168
Sex	M	M	M	F	M
IQ	84	63	65	66	70
Prenatal features	-	-	<u>Hydrocephalus</u>	-	-
Gestation (weeks)	40	37	34	40	40
Birth weight (g)	3835	2600	2629	3515	3840
Perinatal features	<u>Fetal distress</u>	<u>Apgar 5 at 5 mins</u>	<u>Blue turns after birth</u>	-	-
Postnatal features	-	-	-	-	-
Other medical features	Height and weight also >97th centile	>3 Dysmorphic features	-	-	-
Parental retardation	-	-	-	+	-

SUMMARY

i. With the exception of the child with hydrocephalus and possibly the two brothers, macrocephaly was considered to be an incidental finding in study children although the prevalence (6.5%) was greater than expected.

ii. Occipito cranial circumference was measured in the group of schoolchildren used as controls for minor dysmorphic features; 2 out of 55 (4%) had macrocephaly. There was no significant difference in prevalence of macrocephaly in the two groups.

(DF = 1: $\chi^2 = 0.6$: $p > 0.50$)

4. EPILEPSY

Twenty-seven (16%) of the 169 study children had had 1 or more epileptic fits - Table VII.6.

TABLE VII.6

Fits with a predisposing factor		16
CNS infection	4	
Metabolic disorder	1	
Head injury	2	
Pertussis immunisation	1	
Pyrexia	8	
'Idiopathic' epilepsy		10
Infantile spasms		1

Table VII.7 summarises the findings in these children.

TABLE VII.7

Details of epilepsy and other features in 27 out of 169 ESN/M children

Case No.	CNS Infection (4)				Metabolic disorder (1)
	1	74	79	164	115
Sex	M	F	F	F	F
IQ	66	58	70	80	64
Prenatal factors	-	<u>Toxoplasmosis</u> at 14 weeks gestation	Repeated bleeding; ruptured membranes at 30 weeks' gestation	Hyperemesis for 6 months	<u>Adreno-genital</u> <u>syndrome</u>
Perinatal factors	-	-	-	-	-
Postnatal factors	<u>Haemophilus</u> <u>meningitis</u> aged 9 wks. L subdural purulent effusion	-	<u>Meningitis</u> at 6 weeks- CNS irritability No organism found	<u>Encephalitis</u> at 3 years	AGS poorly controlled
Other factors	-	Choroid retinitis Ataxia Precocious puberty Suprasellar calcification	-	-	Congenital glaucoma Anomaly 4th rib
Epileptic history	Grand mal till 18 months old	Grand mal fits at 3,4,6,9,yrs	Fits at time of illness- none since	Continuing Grand mal fits-about 1 per month	Grand mal at 2 months - L. facial palsy developed at same time
Behaviour problems	+	+	-	+	-
Parental retardation	-	-	-	-	-

TABLE VII.7 (continued)

Details of epilepsy and other features in 27 out of 169 ESN/M children				
	Head injury (2)		Immunisation (1)	Infantile spasms (1)
Case No.	49	113	71	118
Sex	F	M	M	F
IQ	60	63	75	61
Prenatal factors	-	Twin	Threatened labour at 24 weeks	-
Perinatal factors	-	Breech delivery at 36 weeks gestation. Jaundice	-	Gestation 35 weeks Twitching after birth for 3 days
Postnatal factors	Head injury at 15 months Bilateral subdural haematoma removed at 17 months	Head injury at 15 months-3 hospital admissions in infancy for gross failure to thrive and lack of maternal care	Reaction to pertussis immunisation	Infantile spasms from 2 weeks old for 2 weeks
Other factors	L.hemiplegia Poor peripheral vision. Perceptual problems	Small stature	-	-
Epileptic history	Grand mal from 15-17 months	2 Grand mal fits in week after head injury	2 Grand mal fits following 2nd pertussis immunisation	Infantile spasms
Behaviour problems	-	-	-	-
Parental retardation	-	+	+	-

TABLE VII.7 (continued)

Details of epilepsy and other features in 27 out of 169 ESN/M children				
Febrile fits (8)				
Case No.	21	34	35	41
Sex	M	M	F	M
IQ	68	58	74	N/A
Prenatal factors	<u>46,XXYY</u>	-	<u>46,X,t(X;19)</u> Alcoholism Bleeding at 16 weeks	Toxaemia
Perinatal factors	-	-	Hypotonic Tube fed for 3 weeks	Gestation 33 weeks. Jaundice <u>Cyanotic turns</u>
Postnatal factors	-	-	-	-
Other factors	-	Macrocephaly	-	Odd appearance Epileptic father
Epileptic history	2 fits aged 2 and 3 years	2 fits aged 2 and 3 years	2 fits aged 9 and 10 months	1 fit aged 14 months
Behaviour problems	+	-	-	-
Parental retardation	-	-	-	+

TABLE VII.7 (continued)

Details of epilepsy and other features in 27 out of 169 ESN/M children				
Febrile fits (8)				
Case No.	55	99	114	141
Sex	F	F	M	F
IQ	74	63	58	60
Prenatal factors	-	APH at 28 weeks	Twin	-
Perinatal factors	Small-for-dates	-	Gestation 36 weeks	<u>Fetal distress</u>
Postnatal factors	-	-	3 hospital admissions in infancy for gross failure to thrive and lack of maternal care	-
Other factors		>3 dysmorphic features. Small stature	-	-
Epileptic history	1 fit aged 8 months	1 fit aged 2 years	1 fit aged 5 months	2 fits aged 3 years
Behaviour problems	-	-	-	+
Parental retardation	+	-	+	-

TABLE VII.7 (continued)

Details of epilepsy and other features in 27 out of 169 ESN/M children					
Idiopathic epilepsy (10)					
Case No.	61	32	69	80	101
Sex	F	M	M	F	M
IQ	70	70	78	68	73
Prenatal factors	Diabetic mother	-	Anaemia Mild toxæmia	Birth weight <10th centile	-
Perinatal factors	-	-	Precipitate delivery	-	Gestation 34 weeks Apgar 5 Apnoeic for 3 minutes Respiratory distress syndrome
Postnatal factors	-	-	-	-	Failure to thrive
Other factors	Obese	Macrocephaly	>3 dysmorphic features	Skull asymmetry	Severe myopia R. Simian crease Anomaly R.5th rib
Epileptic history	2? febrile fits at 2 yrs followed by 9 spontaneous grand mal fits over next year. On phenobarbitone for 2 yrs.	Grand mal from 5 yrs, on sodium valproate.	Petit mal from 5 yrs. On sodium valproate.	2 grand mal fits at 7 yrs EEG-normal.	2 grand mal fits at 22 and 23 months On phenytoin till aged 4 yrs. EEG-normal
Behaviour problems	-	-	+	+	+
Parental retardation	+	+	-	-	-

TABLE VII.7 (continued)

Details of epilepsy and other features in 27 out of 169 ESN/M children					
Idiopathic epilepsy (10)					
Case No.	124	139	12	48	59
Sex	M	M	M	M	M
IQ	59	52	68	70	48
Prenatal factors	Toxaemia Placental insufficiency	-	-	-	46,XY,t(3:15)
Perinatal factors	Brow presentation at 37 weeks- forceps delivery Jaundice. Hypotonic	<u>Apgar score</u> <u>6 at 5 mins</u>	-	<u>Twitching</u> <u>on day 3</u>	-
Postnatal factors	-	<u>Apnoea for</u> <u>20 mins at 3 weeks</u> Poor speech	-	-	-
Other factors	OFC >97th centile	-	-	-	>3 dysmorphic features- long face, high palate. Clinodactyly
Epileptic history	Febrile fit at 14 months- <u>status epilepticus</u> <u>for 3 days.</u> 15 fits next year - none since. Anticonvulsants till aged 4 yrs. EEG-normal	Grand mal from 8 yrs. On sodium valproate. EEG- paroxysmal disturbance.	Grand mal- started at 8 yrs. On sodium valproate. Abnormal EEG	Grand mal from 3 yrs On sodium valproate Abnormal EEG.	Dizzy, shaking spells from 2 yrs. On carbamazepine Abnormal EEG
Behaviour problems	+	+	+	-	+
Parental retardation	-	-	-	-	-

COMMENTS

a. Prevalence

There was a marked increase in the prevalence of epilepsy in study children over that of children in general. In a large survey in Rochester, Minnesota, *Hauser (1975)* found epilepsy in 14 out of 4,914 (0.2%) males and 6 out of 4,714 (0.12%) females, in children aged 1-9 years. This did not include children with febrile fits. In an earlier survey in Carlisle, *Brewis (1966)* found epilepsy (again excluding febrile fits) in 36 out of 11,031 (0.3%) of children aged 0-9 years. The corresponding figure in study children was 19 out of 169 (11.2%). This high prevalence was not unexpected.

Epilepsy is an accepted outward sign of cerebral irritation or damage. The prevalence in severe mental retardation is high. *Primrose (1966)* in a Scottish survey, found epilepsy in 33% of 'idiots', with a gradual decrease in prevalence in those less severely retarded - 20% of 'imbeciles' had epilepsy and 11% of the 'feeble-minded'; this last prevalence is similar to our study population. Although less than 5% of adult epileptics are retarded, *Pond (1965)* found that a third of school age children with epilepsy had educational problems. Epileptics as a group are less intelligent than non-epileptics (*Cooper, 1965.*), and the link between epilepsy and mental retardation is recognised.

b. Sex distribution

This was equal - 4 boys - 4 girls - in those children with febrile convulsions.

Excluding febrile fits 8 out of 72 girls (11%) and 10 out of 97 (10%) boys had had fits. This sex distribution differs from that in the

Rochester survey, (*Hauser, 1975*) where the prevalence of epilepsy in males was almost twice that in females, in unselected children aged 1-9 years. Does this suggest that girls with epilepsy are more likely to be educationally subnormal? The present survey was not large enough to draw any conclusions about this.

However, there was a sex differential in children whose epilepsy was not linked to a specific predisposing factor - of 10 children with 'idiopathic' epilepsy, 8 were male. *Pond (1960)* found a male : female distribution in this group, (with idiopathic epilepsy) of 10 : 4.

c. Intelligence scores

The mean IQ of 16 children with chronic epilepsy was 65.8, slightly lower than the overall mean of 68 in all study children, but with an S.D. of 6.6 this was not significant. (Table III.2)

The mean IQ of 9 children with short-lived epilepsy was not a contributory factor to epilepsy in study children.

d. Severe cerebral insult

In 6 study children fits had started with a cerebral insult and had continued for an extended period - months or years - following metabolic disturbance [15], CNS infection [1, 74, 79, 165.] or head injury [49]. In these children it is reasonable to conclude that the identified cerebral insult had led both to epilepsy and mental retardation. Neurological complications in cases [15, 49] and behaviour disturbances (*Section VII.5*) in the other 4 provide further evidence of cerebral insult.

e. Minor cerebral insult

Fits in 2 children were limited to 1 week following the cerebral insult - in case [56] following head injury and case [71] following pertussis immunisation. This suggests that cerebral damage, if any, was transient, and that although the epilepsy could be attributed to the cerebral insult, their mental retardation could not. Neither of the children had neurological signs nor behavioural disturbance.

f. Febrile convulsions

Febrile convulsions are not, in general, regarded as 'true' epilepsy but rather a reaction of the CNS to pyrexia. No link has been found between febrile convulsions in early life and subsequent retardation. *Hauser, (1975)* in the Rochester survey referred to above, found that 3.2% children under 5 years had febrile convulsions. Eight out of 169 (4.7%) study children had been affected - there was no marked increase in the prevalence of febrile convulsions. Only 1 child [34] in this group had no other feature which could possibly have contributed to mental retardation. The occurrence of febrile fits in study children is likely to be a coincidental feature.

g. Idiopathic epilepsy

There were 10 children with epilepsy which could not be firmly linked to a predisposing factor. Possible aetiological links in 5 of these children were neonatal twitching [48], early apnoea [101, 139], status epilepticus [124] and febrile fits at 2 years [61] which continued as spontaneous seizures over the next year.

Four other children [32, 59, 69, 80.] had abnormal skull shape, which suggested that cerebral development had not been straight forward.

Although no cause was apparent, the mental retardation, epilepsy and dysmorphology in these children could have a common origin.

In only 1 child [12] was there no concomitant medical feature. His grand mal had started at 8 years of age, following admission to the ESN/M school, but may have been a late manifestation of an early, unidentified, cerebral insult.

h. Infantile spasms

Infantile spasms have a recognised association with mental retardation. *Jeavons (1970)* followed up 80 cases; only 13 had made a complete recovery. On a follow-up study after 5 years, 41 were severely retarded, 20 moderately retarded and 6 children mildly retarded. There were no other medical or familial factors in the study girl [118] affected, and I have associated her IQ of 61 with the history of infantile spasms.

i. Family history of epilepsy

i. One child [41] with febrile fits had an epileptic parent - his father, who was also ESN/M. None of the other survey children with epilepsy had an affected parent.

ii. Of 157 mothers in the survey, 2 had a history of epilepsy. None of 7 children born to these 2 mothers had had fits. One mother, on phenytoin and phenobarbitone had had fits since childhood. She had been slow at school, but did not receive special education. Her son [83] was not dysmorphic and had nothing abnormal in his medical history. He had 3 normal brothers, but 1 sister was ESN/M.

The other mother had developed epilepsy in adolescence, was on phenytoin and phenobarbitone from 14 to 20 years of age. A normal son was born when she was 24; the ESN/M son [6] was born 5 years later. He had scoliosis, macrocephaly and facial asymmetry, and is included in the group with dysmorphic features. Pregnancy and labour were normal, and there was no familial retardation.

Speidel (1972) found mental subnormality in 1.5% of 383 children born to 186 epileptic mothers, but in 0.2% of 442 children of 180 controls. However, with just 2 epileptic mothers - and just one on medication - in the survey, any possible increased risk of mental retardation in children of epileptic mothers did not appear to be a contributory factor in this group of ESN/M children.

SUMMARY

1. The prevalence of epilepsy in study children (11.2%) was significantly higher than in the general population (0.2%). This does not include children with febrile fits.

2. Sixteen study children had long-standing epilepsy which may have been linked to their mental retardation.

In 6 of these children epilepsy started immediately after a recognised cerebral insult, of infection or head injury.

Five children with long-standing epilepsy had no overt immediate predisposing factors. One child developed status epilepticus, and chronic epilepsy thereafter, and four had a previous history of apnoea, neonatal twitching or febrile fits.

Four other children had abnormal skull shapes.

One child had no other medical findings.

3. The prevalence of febrile convulsions in study children (4.7%) did not differ significantly from that in the general population (3.2%).

4. Infantile spasms, which had been recorded in just one child, have been regarded as a significant aetiological factor in her retardation.

5. There was no sex differential in children whose epilepsy had an identified precipitating factor, nor in those with febrile fits, but 8 of 10 children with idiopathic epilepsy were male.

6. A family history of epilepsy was not a contributory factor to epilepsy in study children.

5. BEHAVIOUR DISORDERS

Twenty-one children - 12 boys , 9 girls - were recognised as having abnormal patterns of behaviour by both parents and school staff. Fourteen had been seen by a child psychiatrist, Dr L Bartlett, prior to the study. They, and features of behaviour in the other 7 were discussed retrospectively with Dr Bartlett, and coded according to the classification used in the *Diagnostic and Statistical Manual (DSM III) of the American Psychiatric Association (1980)*.

Relevant codes are -

- 299.00 - Infantile autism
- 307.30 - Atypical stereotyped movement disorder
- 312.00 - Conduct disorder, aggressive
- 312.10 - Conduct disorder, unsocialised, non-aggressive
- 314.01 - Attention, deficit disorder, with hyperactivity

Associated features are summarised in Table VII.8.

Individual case details are given Table VII.9.

i. Referral

The possibility that children with behaviour disorders may be referred more readily for special education has already been discussed. *Section III, A, 7* . As the prevalence of behaviour disorders was higher in children with IQs <70 than in those with IQs >70, difficult behaviour did not appear to have influenced referral.

TABLE VII.8

Features of probable/possible association with behaviour disorder
in 21 out of 169 ESN/M children.

<u>Features of probable association</u>	No.	Male	Female
48,XXYY	1	1	-
CNS infection	3	1	2
Prolonged apnoea	3	3	-
Status epilepticus	1	1	-
TOTAL	8	6	2

Features of possible association

Skull/facial dysmorphology	6	3	3
Perinatal asphyxia	2	-	2
Short stature and poor parental rapport	2	2	-
Idiopathic epilepsy	1	1	-
TOTAL	11	6	5

No other features

	2	-	2
TOTAL	1	-	2

TABLE VII.9

Findings in 21 out of 169 children with behaviour disorders.

Case No.	1	4	6	12	21	26
Sex	M	M	M	M	M	F
IQ	66	-	86	68	68	-
Prenatal factors	-	-	-	-	<u>48,XXYY</u>	-
Perinatal factors	-	C/S for placenta praevia	-	- (Home delivery)	-	-
Postnatal factors	<u>Haemophilus meningitis</u> aged 9 weeks	-	-	-	-	-
Other medical features	-	Short stature	Macrocephaly >3 dysmorphic features	-	-	Very little speech
Behaviour (DSM III Class.)	Aggressive (312.10)	Autistic (299.00)	Labile hyperactive (312.10)	Aggressive (312.10)*	Unpredictable aggressive (312.00)	Autistic (299.00)*
EEG	-	-	Abnormal r.cortex	Abnormal	-	-
Epilepsy	-	-	-	+	-	-
Parental retardation	-	-	-	-	-	-
Home background	Good	Poor	Average	Average	Good	Good

* Not seen by psychiatrist

TABLE VII.9 (continued)

Findings in 21 out of 169 children with behaviour disorders.					
Case No.	42	53	59	68	69
Sex	F	M	M	F	M
IQ	79	66	48	77	78
Prenatal factors	Ovran for 4/12 toxaemia	-	46,XY,t (3:15)	<u>Microcephaly</u>	Maternal anaemia
Perinatal factors	-	-	-	-	Rapid delivery
Postnatal factors	-	-	-	Jaundice	-
Other medical features	Odd facial appearance	Short stature	Odd facial appearance >3 dysmorphic features	Mild cerebral palsy	>3 dysmorphic features
Behaviour (DSM III Class.)	Labile hyperactive (312.10)*	Obsessive inconsistent (312.10)*	Hyperkinetic difficult to control (312.10)	Labile (312.10)	Restless Autistic echolalia (312.10)
EEG	-	-	Abnormal	-	Abnormal
Epilepsy	-	-	+	-	+
Parental retardation	-	-	-	-	-
Home background	Good	Poor	Average	Good	Good

* Not seen by psychiatrist

TABLE VII.9 (continued)

Findings in 21 out of 169 children with behaviour disorders.					
Case No.	74	80	101	117	124
Sex	F	F	M	M	M
IQ	58	68	73	71	59
Prenatal factors	<u>Toxoplasmosis</u>	Poor weight gain-birth weight <10th centile	Gestation 34 weeks	-	Toxaemia Placental insufficiency
Perinatal factors	-	-	<u>Apgar score 5</u> apnoea for 3 mins Respiratory distress syndrome	Rapid delivery	Forceps for brow presentation Jaundice
Postnatal factors	-	-	-	<u>Apnoea at 6 months</u>	<u>Status epilepticus at 14 months</u>
Other medical features	Poor vision Ataxia, precocious puberty	Asymmetric skull and face	R. Simian crease	-	OFC >97th centile
Behaviour (DSM III Class.)	Unpredictable (312.10)*	Hyperactive Autistic echolalia (312.10)	Restless difficult self-mutilating (307.30,312.10) (314.01)	Difficult to control unpredictable (312.10)*	Inappropriate unresponsive (312.10)
EEG	-	Normal	Normal	-	Normal
Epilepsy	+	+	+	-	+
Parental retardation	-	-	-	-	-
Home background	Good	Average	In care	Average	Good

* Not seen by psychiatrist

TABLE VII.9 (continued)

Findings in 21 out of 169 children with behaviour disorders.					
Case No.	139	141	142	150	164
Sex	M	F	F	F	F
IQ	52	60	66	60	80
Prenatal factors	-	-	Toxaemia	Hyperemesis Debendox	Hyperemesis
Perinatal factors	<u>Apgar 6</u>	<u>Fetal distress</u>	-	<u>Fetal distress</u>	-
Postnatal factors	<u>Apnoea at at 3 weeks</u>	-	-	-	<u>Encephalitis aged 3 yrs</u>
Other medical features	Speech severely retarded	-	-	Coarse facial features	-
Behaviour (DSM III Class.)	Disorientated restless (312.10)	Hyperactive screaming attacks (312.10)	Difficult unresponsive (312.10)*	Aggressive destructive (312.10)	Disruptive (312.10)
EEG	Abnormal	-	-	-	-
Epilepsy	+	Febrile fits	-	-	-
Parental retardation	-	-	-	-	-
Home background	Good	Average	Poor	Good	Average

* Not seen by psychiatrist

ii. Aetiology

In 8 study children, the conduct behaviour disorder was probably linked to the same aetiological medical factor as the retardation.

Aggressive, impulsive behaviour is common, although not invariable in boys with an XYY karyotype. [21]. (*Borgaonkar, 1970*).

The child [74] with congenital toxoplasmosis had always had somewhat unpredictable behaviour. In 2 children [1, 164] with postnatal infections of the CNS, development and behaviour were disturbed only subsequent to the infection.

Episodes of apnoea in early life in cases [101, 117, 139.] had probably contributed to the behaviour disorder and the retardation. One child [73] had been apnoeic for 3 minutes at birth at 34 weeks' gestation. In the first two months of life he had repeated respiratory infections. He was restless, unable to concentrate, and his face, arms and hands bore numerous self-inflicted scratches and other lesions. Another child [117] could be unresponsive or aggressive - as he was when seen on the first school visit, but was liable to mood swings and on another occasion when seen was pleasant and cooperative. The third child [139] with prolonged apnoea, had little rapport, either physical or mental, with his surroundings. He could not remember where the various rooms and stairs at school were, had to be guided about by a member of staff. He was uncommunicative, and appeared to have very little memory for past events. Teaching staff felt he would require to attend a school for the severely sub-normal.

The child [124] with prolonged status epilepticus was also unresponsive. He appeared to live in a fantasy world, and reacted inappropriately to external stimuli. When asked to take off his shoes and socks for examination, he replied that this would cause a

bomb in his school to explode - but he appeared oblivious to having a blood sample taken.

Two other children with behaviour disorders had had recorded fetal distress. One child [141] had never established a regular sleep pattern, had unpredictable outbursts of screaming: and at the age of 8 years, had no sense of danger from road traffic or heights.. The other child [150] was born at 42 weeks' gestation, by an emergency Caesarean section for fetal distress. She was given oxygen at delivery, but was in special care for less than a day. As a baby she was noted to have bizarre movements of her head, arms and legs. She had coarse facial features (*Appendix photograph*) and was difficult to control. Her only sibling, a boy, had similar facial features and behaviour disturbance, attended an ESN/S school. Both children had been investigated for metabolic disorders, with negative results.

In these latter two study children, any link between prenatal asphyxia and the behavioural disturbance is not so evident. Fetal distress has been accepted in this study as a probable contributory cause to mental retardation. One could argue that if the cerebral insult from prenatal asphyxia is thought sufficient to contribute to mental retardation, it could also give rise to a behaviour disorder. However, 8 other survey children had recorded fetal distress - and normal behaviour. Hence, while the link may be present, I have left it as 'possible'.

Unidentified factors in prenatal or early postnatal life may have contributed to both mental retardation and behaviour disturbance in 6 other children who had abnormal skull shape and/or facial features. One [68] of these children had microcephaly, another [6] was macrocephalic. He and another two boys [59. 69] had 3 or more dysmorphic features.

Two boys with behaviour disorders were of small stature. Neither had had intrauterine growth retardation. One [4] was very subdued, with autistic features. It had not been possible to assess his IQ. His parents were intelligent, with university degrees, but the impression at the home visit was that he was paid scant attention. The mother of the other child [53], who had a marked obsession with time and numbers and inappropriate behaviour, felt that she had not 'bonded' with him after birth and said she much preferred his younger brother.

One boy [12] had idiopathic epilepsy, with an abnormal EEG. He was liable to unprovoked aggressive outbursts. His mental retardation, abnormal behaviour and epilepsy may have stemmed from the same unidentified source. One child [53] had no other medical factors, and had caring parents. She had obsessive, autistic behaviour, very little intelligible speech and was greatly disturbed by any change in routine. It had not been possible to perform a formal assessment of intelligence.

iii. Sex distribution

There was no appreciable sex difference in the behaviour disorders in study children with nine out of 72 (12.5%) girls, and 12 out of 97 (12.3%) boys being affected.

iv. Intelligence scores

Formal IQ assessment had not been done on 2 children, both with autistic features. The average IQ was 67.5 - close to the average of 68 in all study children.

v. Epilepsy

Nine children with behaviour disorders had epilepsy - excluding febrile fits. In 5 [58, 73, 124, 139, 164.] of these, the epilepsy resulted from a known cerebral insult.

One child [12] had idiopathic epilepsy, and no other features. However, in 3 children [59, 69, 80.] the combination of behaviour disorder, epilepsy, and dysmorphic facial and skull features is suggestive of a pathological - but unidentified-basis for their mental retardation.

vi. Family background

Three children [4, 53, 142] had parents who expressed a lack of bonding or empathy with their ESN/M children. All three had just one sibling with whom, in each case, the parents felt they had better rapport. In two of these children [4,53] the lack of bonding was from early infancy. In the third child [154], a girl aged 11 years, the lack of rapport had developed over the last few years and may have been a consequence of the behaviour disorder.

No parents of any children with behaviour disorders had had educational problems. This feature is discussed below (*Section VIII,5*). Overall, parents of 86% of study children had had learning difficulties. Children whose parents were of low educational attainment might perhaps be referred less often to a psychiatrist - but not all children with behaviour disorders had actually been referred. Assessment by both parents and staff was also considered. The lack of educational problems in the parents of this group of children suggests the possibility of a common aetiology, in gestation, delivery, or infancy, for both the behaviour disorder and the retardation.

SUMMARY

1. In 8 of the 21 study children the behaviour disorder was probably linked to an identified medical aetiological factor. It was not felt that perinatal asphyxia, recorded in 2 other children could be linked with the behaviour disorder.
2. Six other children had facial and/or skull dysmorphology suggestive of underlying but unidentified pathology.
3. Two children had short stature, possibly linked to their behaviour disorder.
4. Epilepsy was also present in 9 children. In 3 children, a combination of behaviour disorder, epilepsy and facial/skull dysmorphology was present.
5. One child, with marked autistic behaviour, had no other medical features noted. In another girl with difficult negative behaviour, maternal toxemia was the only medical factor.
6. There was no sex differential in behavioural problems, which occurred in 12.5% girls, 12.3% boys.
7. Intelligence scores - it has already been noted that (*Section III, A, 7*), behavioural disturbance was not more common in children with IQs >70 than in those with IQs <70. The average intelligence score in children with behaviour disorders did not differ from that of the study group overall.
8. It was of interest to note that no children with behaviour disorders had parents who had had educational problems. In the study overall, parents of over half the study children had themselves had learning problems.

SECTION VII - INCOORDINATION

Methods used in assessing testing for the presence of incoordination are discussed in *Section IV, 3 b.*

Three children did not cooperate sufficiently to be tested - 2 children [4,26] with autistic behaviour, and one child [122] with microcephaly.

Interpretation of the tests used is subjective, and could be affected by observer bias. The medical background was already known when the children were tested.

Results

The prevalence of incoordination in study and control children is shown in Table VII.10. Details of individual children with incoordination are given in Table VII.11.

TABLE VII.10

Prevalence of incoordination in ESN/M children
and control children

	Total	No. with incoordination (%)
Study children	166	42 (25)
with medical risk factors of probable significance*	70	26 (37)
with medical risk factors of possible significance*	61	11 (18)
with no identifiable medical risk factor	35	5 (14)
Control children	55	4 (7)

*1 and *2 children in these groups were not tested for incoordination

TABLE VII.11

Findings in 42 out of 166 ESN/M children with incoordination.

a.26 children with medical aetiological features probably associated with mental retardation/incoordination.

Case No.	<i>Chromosomal (4)</i>		<i>Prenatal (10)</i>		<i>Genetic syndrome (2)</i>	
	7	21	111	133	63	154
Sex	M	M	F	F	M	M
IQ	69	68	74	64	58	61
Chromosome	<u>46,XY,14q+</u>	<u>48,XXYY</u>	<u>47,XX+21</u>	<u>47,XX+21</u>	-	-
Genetic syndrome	-	-	-	-	<u>Sotos</u>	<u>Rubenstein-Taybi</u>
Behaviour disorder	-	+	-	-	-	+
Epilepsy	-	Febrile fits	-	-	-	-
Prenatal factors	-	-	Hyperemesis	-	-	-
Perinatal factors	Jaundice	-	-	-	Gestation 36/52	Jaundice
Postnatal factors	-	-	-	-	-	-
Uncertain origin	-	-	-	-	-	-
Parental retardation	-	-	-	-	+	-

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

a. 26 children with medical aetiological features probably associated with mental retardation/incoordination.

	<i>Cerebral malformation (2)</i>		<i>Prenatal (10) Metabolic disorder (1)</i>	<i>Intrauterine infection (1)</i>
Case No.	68	134	115	74
Sex	F	F	F	F
IQ	77	55	64	58
Cerebral malformation	<u>Microcephaly</u>	<u>Microcephaly</u>	-	-
Metabolic disorder	-	-	<u>Adreno-genital syndrome</u>	-
Intrauterine infection	-	-	-	<u>Toxoplasmosis</u>
Behaviour disorder	+	-	-	+
Epilepsy	-	-	+	+
Prenatal factors	-	Toxaemia Small-for-dates	-	-
Perinatal factors	Jaundice	-	Salt loss	-
Postnatal factors	-	-	poor control	-
Uncertain origin	>3 Dysmorphic features	-	-	-
Parental retardation	-	+	-	-

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

a. 26 children with medical aetiological features probably associated with mental retardation/incoordination.

Perinatal (13)
Fetal distress (5)

Case No.	43	119	141	147	150
Sex	M	F	F	M	F
IQ	-	73	60	80	60
Behaviour disorder	-	-	+	-	+
Epilepsy	-	-	Febrile fits	-	-
Prenatal factors	Small-for-dates	-	-	Bleeding at 3-4 months	Hyperemesis Debendox
Perinatal factors	-	-	-	-	-
Postnatal factors	-	-	-	-	-
Uncertain origin	Small stature Poland's anomaly cleft lip/palate	-	-	>3 Dysmorphic features	-
Parental retardation	-	+	-	-	-

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

a. 26 children with medical aetiological features probably associated with mental retardation/incoordination.

*Perinatal (13)**Apgar score equal to or less than 6 at 5 minutes (5)*

Case No.	11	31	90	101	156
Sex	M	M	M	M	M
IQ	83	60	52	73	67
Behaviour disorder	-	-	-	+	-
Epilepsy	-	-	-	+	-
Prenatal factors	-	Hyperemesis	-	-	-
Perinatal factors	-	-	-	Gestation 34/52	-
Postnatal factors	-	-	-	-	-
Uncertain origin	-	-	-	R. Simian crease Rib anomaly	-
Parental retardation	-	-	+	-	+

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

a. 26 children with medical aetiological features probably associated with mental retardation/incoordination.

Case No.	<i>Cyanosis (2)</i>		<i>Perinatal (13)</i> <i>Twitching (1)</i>
	23	41	48
Sex	M	M	M
IQ	73	-	70
Behaviour disorder	-	-	-
Epilepsy	-	Febrile fits	+
Prenatal factors	Toxaemia	Toxaemia	-
Perinatal factors	-	-	-
Postnatal factors	-	-	-
Uncertain origin	-	-	-
Parental retardation	-	+	-

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

a. 26 children with medical aetiological features probably associated with mental retardation/incoordination.

Case No.	<i>CNS infection (1)</i>	<i>Postnatal (3) CNS trauma (2)</i>	
	1	49	124
Sex	M	F	M
IQ	66	60	59
CNS infection	<u>Haemophilus meningitis</u>	-	-
CNS trauma	-	<u>Head injury</u>	<u>Status epilepticus</u>
Behaviour disorder	+	-	+
Epilepsy	+	-	+
Prenatal factors	-	-	Toxaemia Placental insufficiency
Perinatal factors	-	-	Jaundice
Postnatal factors	-	-	-
Uncertain origin	-	>3 Dysmorphic features	Macrocephaly
Parental retardation	-	-	-

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

b. 11 children with medical features possibly associated
with retardation/incoordination.

Case No.	6	12	16	25	32	53
Sex	M	M	M	F	M	M
IQ	86	68	74	75	70	66
Behaviour disorder	+	+	-	-	-	+
Epilepsy	-	+	-	-	+	-
Prenatal factors	-	-	Anaemia Small-for-dates	-	-	-
Perinatal factors	-	-	-	-	-	-
Postnatal factors	-	-	Excessive weight loss	-	-	-
Uncertain origin	Macrocephaly >3 Dysmorphic features	-	-	Small stature	Macrocephaly	Small stature
Parental retardation	-	-	+	-	+	-

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

b. 11 children with medical features possibly associated
with retardation/incoordination.

Case No.	59	60	69	103	130
Sex	M	M	M	M	M
IQ	48	63	78	69	76
Behaviour disorder	+	-	+	-	-
Epilepsy	+	-	+	-	-
Prenatal factors	46,XY,t (3:15)	-	-	-	Fall+show at 32/52
Perinatal factors	-	Gestation 36/52	Precipitate delivery	Gestation 34/52	-
Postnatal factors	-	Jaundice	-	-	-
Uncertain origin	>3 Dysmorphic features	-	>3 Dysmorphic features	Small stature	-
Parental retardation	-	+	-	-	-

TABLE VII.11 (continued)

Findings in 42 out of 166 ESN/M children with incoordination.

c. 5 children with no associated medical features.

Case No.	47	54	62	67	123
Sex	M	F	M	F	F
IQ	51	81	74	56	57
Behaviour disorder	-	-	-	-	-
Epilepsy	-	-	-	-	-
Prenatal factors	-	-	-	-	-
Perinatal factors	-	-	-	-	-
Postnatal factors	-	-	-	-	-
Uncertain origin	-	-	-	-	-
Parental retardation	+	-	+	-	-

TABLE VII.12

Incoordination in 137 ESN/M children -with, and without, recorded perinatal stress, and with no significant pre- or post-natal aetiological features.

	Total No.	No. with incoordination
Recorded perinatal stress	41	13
No recorded perinatal stress	96	14
DF = 1 : $\chi^2 = 5.3$: 0.05 > p > 0.02		

TABLE VII.13

Incoordination in 46 ESN/M children with specific perinatal risk factors.

Factor	Total no.	Incoordination	No incoordination
Fetal distress	10	5	5
Apgar score equal to or less than 6 at 5 minutes	16	5	11
Blue/limp at birth	4	0	4
Cyanosis in first few days	11	2	9
Twitching in first few days	5	1	4
Total	46	13	33

COMMENTS*i. Prevalence - shown in Table VII.10.**a. Overall prevalence*

Forty two out of 166 (25%) study children had incoordination. This study is comparable to that of *Hagberg (1981)* in 91 Swedish children with MMR, of whom 23% had incoordination.

b. Prevalence in relation to medical features

Incoordination was twice as common in study children with identified medical aetiology as in children with medical features of possible relevance. The difference in these 2 groups was significant.

$$(DF = 1: x^2 = 5.8 : 0.02 > p > 0.01).$$

This finding would appear to underline the possibility that incoordination may be regarded as further evidence of cerebral dysfunction in children with MMR.

The control children had the lowest prevalence - 7%, half that in study children where no medical factor was found. However, this difference was not significant.

$$(DF = 1: x^2 = 1.16 : 0.5 > p > 0.10).$$

ii. Intelligence scores

The average IQ in this group of children with incoordination (70.2) was similar to that of study children overall (68). Incoordination with an identified cerebral insult was not more common in children in the lower IQ ranges.

iii. Sex

Sex distribution of children with incoordination and an identified pre- or post-natal insult was equal (6 boys, 7 girls). Where a perinatal insult had occurred, 11 boys and 2 girls had incoordination. However, against a total of 30 boys, and 16 girls with perinatal asphyxia, this sex difference was not significant.

$$(DF = 1: \chi^2 = 3.0 : 0.10 > p > 0.05).$$

iv. Medical features of probable aetiological significance

a. Prenatal features

There were 9 children with disorders of prenatal origin of probable association with their retardation, in whom the presence of incoordination is likely to be another sign of some impairment in brain development. In another child [115] the disorder, adrenogenital syndrome, was also of prenatal origin. Although her brain damage was a secondary, rather than primary, result of her disorder, her incoordination and retardation are likely to be the result of poor salt control which resulted in fits.

(Section V, 4,a).

It was of interest to note that four children with chromosome abnormalities did not have incoordination - 46,XXt (X:19) [35], 46,XX del(15) [107], 47,XXY [40] and 47,XXY [106]. In boys with Klinefelter syndrome, spatial sense and hand-eye coordination tend to be reduced, but this was not evident in the tests used in this survey.

b. Perinatal features

Perinatal asphyxia and incoordination

Of 46 children with perinatal asphyxia, 13 (28%) were found to have incoordination. In looking for a possible relationship between perinatal stress and incoordination in these retarded children I have excluded 30 children with identified pre- and post-natal medical factors of probable significance, which could have contributed both to mental retardation and to incoordination. There were 30 such children; of the remaining 137 tested, 41 had recognised perinatal stress.

Table VII.12 shows the number of children with, and without perinatal stress who showed incoordination.

The prevalence of incoordination was significantly, but not highly significantly, greater in those children who had had perinatal stress ($DF = 1 : \chi^2 = 5.3; 0.05 > p > 0.02$).

Specific perinatal stress features

Table VII.13 shows the number of children with incoordination in each of the 5 risk categories of perinatal stress.

None of the 4 children found blue and limp at birth had incoordination. Half of the children with recorded fetal distress showed incoordination, but fewer than half of the children with low Apgar scores, or who were limp at birth, cyanotic or jittery in the first few days after birth showed incoordination. Numbers in these groups are small, but there was nothing to suggest that any single perinatal risk factor showed a strong association with incoordination.

c. Postnatal features

Of 3 children with postnatal CNS infections, just 1 [13] showed incoordination. Neither the girl [79] with meningitis aged 6 weeks, nor another girl [164] with encephalitis aged 3 years, were affected, although the latter child had had marked behaviour problems since her encephalitis.

The child [49] with a severe head injury at 16 months, and the boy [124] with status epilepticus at 14 months, had incoordination - but it was not evident in the child [14] who had severe pertussis, nor in either of the boys with prolonged apnoea [117, 139].

v. *Medical features of possible aetiological significance*

a. Eleven children with incoordination had medical factors possibly linked to their retardation. (Table VII.10) Although no cerebral insult had been identified, the presence of epilepsy or behaviour disorder in 3 boys [6, 32, 53.] and of both in another 3 boys [12, 59, 69.], is suggestive of some disturbance in cerebral development, with incoordination an additional suggestive feature.

Features noted in the other 5 - maternal injury [130], low birth weight [16], prematurity [60, 103.] and small stature [35] have a less apparent relationship to incoordination and may be coincidental.

b. Sex

This group included just 1 girl [35]. If one accepts that incoordination is a physical sign of cerebral dysfunction, could it be that males are more likely to be retarded as a result of a relatively minor undetected cerebral insult?

vi. No associated medical features

- a. In 5 children, incoordination was the sole medical feature found.
- b. Sex - this group showed no sex differential, with 3 girls, 2 boys.

c. Parental retardation

Parents of 4 of these children had had educational problems. The retardation could have been familial, but one could not say from the study - parents were not examined - whether incoordination was also familial, or due to some other unidentified factor.

The child whose parents were of average intelligence had an IQ of 56: this marked reduction in intelligence combined with incoordination, suggests an undiagnosed cerebral insult.

SUMMARY

i. Forty-two out of 166 study children show incoordination. The presence of incoordination suggests underlying neurological impairment and was regarded as an important physical feature. When minor motor dysfunction and mental retardation co-exist, the likelihood of mental retardation resulting from cerebral pathology is increased.

ii. In 26 out of 42 study children with incoordination, a pathological aetiological factor had been identified.

iii. Incoordination was found significantly more frequently in study children with identified medical aetiology than in those without.

iv. The prevalence of incoordination in study children with negative histories was not significantly higher than in a group of control schoolchildren.

v. In 6 children in whom no aetiological feature was identified, the presence of epilepsy and/or behaviour disorder added further weight to the possibility that their mental retardation was the result of a cerebral insult.

vi. There were 5 children in whom incoordination was the sole medical feature noted, and a further 5 who had minor medical features with no apparent link to incoordination.

vii. No association was noted between incoordination and

- IQ range

- sex

or

- specific perinatal features;

but incoordination was noted more frequently in children with an adverse perinatal history.

SECTION VIII - SOCIAL AND FAMILIAL BACKGROUND

Findings in this section appeared in an article -

*The socio-familial background and prevalence of
medical aetiological factors in children attending
ESN/M schools - M A Lamont
Journal of Mental Deficiency Research - 1988
- 32, 221-232*

A copy of the reprint is in *Appendix C*

The primary aim of this study has been to identify medical causes of MMR, but development in children is dependent on the social and cultural influences to which the child is exposed. A child's motivation for learning will be influenced by the intellectual and emotional support provided at home : children in whom such support is low or lacking are likely candidates for special education, irrespective of any medical aetiology. However, for any given medical insult in early life the final outcome in the level of intellect will depend on a child's initial potential and subsequent socio-cultural influences.

This study therefore includes consideration of the children's social and familial backgrounds. Information collected at the home visits about these is presented and discussed in this section.

Demographic features of social class and family size were quantitatively assessed and related to the population : the sibling position was related to that expected statistically. Such comparisons do not indicate specific aetiological factors but may indicate, if only indirectly, social factors contributing to mild retardation. Social conditions may have a secondary association with mental retardation if they have an association with medical risk factors. Probable medical

risk factors identified in the study are related to social findings in each subsection. Identified medical factors which have no confirmed aetiological link with retardation have been considered only where social circumstances were of possible relevance - e.g. malnutrition, short stature.

A. SOCIAL CLASS

Children were allocated to social groups by the occupation of the head of the household in accordance with the classification used in census reports.

a. SOCIAL CLASS DISTRIBUTION

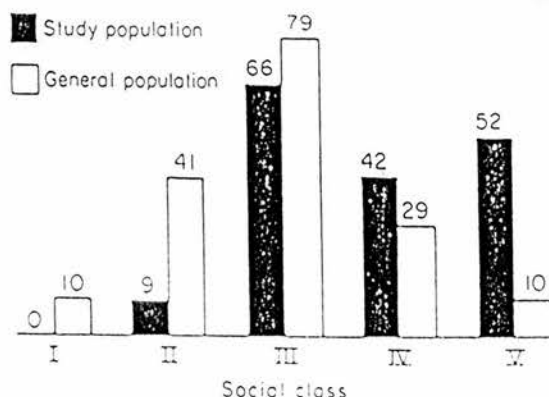
This is shown in *Figure 2*.

There were no children in social class I (expected number 10), and 9 in social class II (expected number 41). In social classes IV and V there was an excess of study children - 94 (56%) as against 39 (23%) expected. This was a highly significant shift in distribution.

($p < 0.001$)

The 1981 census (*HMSO Census of Population Reports. 1984*) gives the percentage of dependent children in each social class in England and Wales. From these percentages, equivalent figures for 169 children were calculated and used as standard for comparison with the study children.

Figure 2 Social class distribution of children attending ESN/M schools and in the general population ($n = 169$).



The lack of children in social class I may reflect use of private education by parents in this group - such parents might have an increased preference for private education for a child who appears to be of below average intelligence. This factor may be operating to a lesser extent, in social class II: there were nine children in this group, considerably lower than the 41 equivalent in the general population. It is not likely to have any significant effect on distribution in social classes III, IV, and V. Sixty-six (39%) children in the survey came from social class III; 94 (56%) from social classes IV and V, as compared to 23% in the general population. With the known association of MMR and lower social class, the shift in social class distribution was not unexpected. It was slightly surprising, however, to find in this study that just 56% of children came from social classes IV and V. In recent studies, 78% of children with MMR in Mannheim were from the lower social classes (*Cooper and Lackus, 1984*); in Montreal (*Larson and Lapointe, 1986*), 94% of 77 adolescents with mild to moderate mental handicap were from social class IV or V.

b. *SOCIAL CLASS AND MEDICAL FACTORS OF PROBABLE AETIOLOGICAL
SIGNIFICANCE*

i. *Overall prevalence*

The prevalence of identified medical risk factors pre-, peri- or postnatal in each social class is shown in Table VIII.1. The overall prevalence of medical features fell from 55% in class II to 30% in class V ($0.05 > p > 0.02$). This significant fall in medical identified risk factors could reflect an increased contribution of non-medical factors to mild retardation in lower social groups, but it is also interesting to note that in social class II just over half the children had identified medical features. Children from social class II could be expected to have a favourable home background and one might have expected a higher prevalence of recognisable medical aetiology. The fact that 45% of these children had no identified medical aetiology underlines how frequently the origin of MMR remains obscure.

ii. *Prenatal factors*

Prenatal factors were identified in 22 (13%) children. No children in social class II had prenatal features; in social class III, IV, and V the prevalence was 15%, 19% and 7.6% respectively. Prenatal features such as chromosome abnormalities or sporadic syndromes associated with mental retardation will occur independently of social class and were found in children from social classes III, IV and V. None were found in children from social class II, but numbers here (9) were low.

TABLE VIII.1

Social class and medical risk factors in 169 ESN/M children

SOCIAL CLASS	<i>n</i>	Prenatal	Perinatal	Postnatal	Total (%)
II	9	0	1	4	5 (55)
III	66	10	20	3	33 (50)
IV	42	8	8	1	17 (40)
V	52	4	12	0	16 (30)

Total	169	22	41	8	71 (42)
-------	-----	----	----	---	---------

Environmental prenatal features of pathological significance had been present in 2 children from social class III [74] - toxoplasmosis and [98] alcohol fetopathy. The excess of study children in social classes IV and V was not the consequence of recognised prenatal pathology contributing to mental retardation.

iii. Perinatal factors

All but 6 of the study children had been delivered in hospital hence social class should have little bearing on perinatal problems. The 6 children delivered at home included 2 from social class II, 2 from social class III, and 1 each from social classes IV and V - there was no social class bias in these home deliveries.

Perinatal features were the most frequent medical association in the study group : overall they had occurred in 46 out of 169 (27%) children. (Table V.9). Children from social classes IV and V were not at greater risk of having suffered perinatal problems - they had been recorded in 20 out of 66 (30% children in social class III; in social classes IV and V the incidence was 19% and 23% respectively. Again, the excess of study children in social classes IV and V could not be attributed to late sequelae of perinatal distress.

iv. Postnatal factors

Of 8 children who had had postnatal events which could have resulted in mental impairment, 4 were in social class II - including a girl [40] with non-accidental head injury which resulted in hemiparesis. The 2 children [117, 139] with prolonged apnoea in early life - "rescued cot deaths" came from social classes III and II. Postnatal events of aetiological significance had occurred in about half - 4 out of 9 - the children in social class II but in only 1 of 94 children in social classes IV and V. There was therefore nothing in study

findings to suggest that children from the lower social classes are at increased risk of being retarded as a result of identifiable medical features in their postnatal environment. .

*c. SOCIAL CLASS AND MEDICAL FACTORS OF POSSIBLE AETIOLOGICAL
SIGNIFICANCE*

From those medical factors found in the study children which presented a possible, as opposed to probable, risk of mental retardation, I have considered in this section only those in which social class might be relevant.

i. Prenatal possible risk factors

ANAEMIA

Anaemia was not a common problem (Table VI.1) - just 4 survey mothers had received parenteral iron. One was the mother of twins [27,28] in social class IV. There were just 2 anaemic mothers in social class V - one of whom had a Prader-Willi child. These small numbers do not suggest that retarded children in social classes IV and V - or II or III - are more likely to be born to anaemic mothers.

SMALL FOR GESTATIONAL AGE

Eleven survey children were small-for-dates, but 7 of these had other features of abnormal prenatal development: four had major abnormalities - Prader-Willi syndrome, microcephaly, cleft lip and palate, fetal alcohol syndrome and Poland's anomaly, and 2 more were twins. Such abnormal features occur independently of social class. One of the remaining 4 was born to a 41 year old mother, with a history of 6 previous spontaneous abortions since her last full term pregnancy 16 years before; the social class - IV - of this family is not likely to be relevant.

The 3 other children were from social classes IV and V, but again, with such small numbers, no link between social class and intrauterine

growth retardation - and hence, possibly, with later mental retardation, was evident.

ii. Perinatal possible risk factors

PREMATURITY

Twenty-one study children had been born at or before 36 weeks' gestation. Seven of these were twins in whom prematurity occurs relatively frequently.

Seven of the other 14 children had mothers in social class V - however, just 2 of these children [41, 118] had had recognised perinatal stress. Thus although prematurity occurred in 14% of study children in social class V, the prevalence of perinatal factors of recognised risk in these children did not suggest any link with mental retardation.

iii. Postnatal possible risk factors

SEVERE MALNUTRITION

The twins [81, 82] who were admitted profoundly underweight from severe neglect at the age of 8 months had very poor home circumstances, with inadequate retarded parents - in social class V. There is an obvious link between this social class and such neglect, but not directly with mental retardation - although such extreme deprivation may have compounded the other adverse features in the boys' background.

INJURY

Just 2 children [113, 152] had had postnatal head injuries with possible long term effects - one from social class III, and one from social class V. As with children whose postnatal medical features were more probably limited to their retardation, social class was not relevant.

iv. Features of uncertain origin

HEIGHT ON OR BELOW THE 3RD CENTILE

Eight of the 30 children with short stature had medical features of probable association (Table VII.2). Of the other 22, 4 came from social classes II and III. Three of these children had behaviour problems of an autistic or obsessional nature. There were 18 children with unexplained short stature from social classes IV (7) and V (11). This increased prevalence of short stature in social classes IV and V may reflect poor home conditions - and delayed physical development may reflect delayed mental development, although the pathogenesis of such stunting is not clear. From these figures, however, social class was of relevance in the physical growth of study children.

BEHAVIOUR DISORDERS

There were 12 children with idiopathic behaviour disorders, of whom just 3 came from social classes IV and V. It could be that referral to a psychiatrist was less likely to be considered for children from lower social class homes, but contact with the children at the school examination did not suggest this. Delayed mental development associated with psychiatric problems was apparently more frequent in children with good physical home circumstances.

SUMMARY

1. There was a significant shift in social class distribution of study children to social class IV and V, but this was less than that found in other surveys.
2. Medical risk factors fell significantly with social class.
3. Medical risk factors - pre-, peri-, and postnatal - of environmental origin - were not more frequent in children living in poor home conditions.
4. Short stature with no evident cause was more frequent in children from social classes IV and V.

2. FAMILY SIZE

The 1981 census (*HMSO Census of Population Reports, 1984*) provides information on the distribution of family size in the general population. From this the expected distribution of family size was calculated for 169 children, and compared with that of study children. Results, with social class distribution, are shown in Table VIII.2.

TABLE VIII.2

Distribution of family size, in relation to the general population and to social class, in 169 ESN/M children

		No of children in family				
		1	2	3	4	5 or more
General population						
(n = 169)		41	71	36	14	7
Study population						
(n = 169)		7	75	35	26	26
Social class	II	1	7	1	-	-
	III	3	40	9	10	4
	IV	-	13	13	10	6
	V	3	15	12	6	16

i. Distribution

There was a shift towards large families in the study population, as compared with the general population. Families of 4 siblings were almost double the expected number.

Families of 5 or more children had almost 4 times the expected prevalence.

None of the 9 study children in social class II came from sibships of more than 3 children.

In social class III, 14 out of 66 (21%) were from large families, in social classes IV and V, 40% children were from sibships 4 - 16 out of 42 (38%) in social class IV and 22 out of 52 (42%) in social class V.

Family size was thus significantly increased in study children, with the prevalence of sibships equal to or greater than 4 in social class V double that in social class III. Large families tend to occur more frequently in lower social classes (*Kushlick and Blunden, 1974*), but even so, they were over represented in the survey.

Children from large sibships have been shown to have lower intelligence ratings than children from sibships of 3 children or less. (*Anastasi, 1956*) and hence will be more prone to overt learning difficulty. Any adverse influence on brain development will enhance this trend.

ii. Medical risk factors

Shown in Table VIII.3.

TABLE VIII.3

Family size and medical risk factors in 169 ESN/M children

	No of children in family			
	1	2	3	4 or more
Total	7	75	35	52
Medical features (% in group)	4 (57)	33 (42)	13 (37)	21 (40)
Prenatal	2 (29)	4 (5)	5 (14)	11 (21)
Perinatal	1 (14)	24 (31)	6 (17)	10 (19)
Postnatal	1 (14)	5 (6)	2 (6)	0 (0)
No medical risk factors	3 (43)	42 (58)	22 (63)	31 (60)

Medical risk factors were identified in 4 of 7 only children.

In siblings of 2, 3, or more than 4, the overall prevalence of medical risk factors was 42%, 37%, and 40% respectively.

This did not suggest that sibship size per se was related to medical risk factors associated with mental retardation, although perinatal problems predominated in children from sibships of two. However, when social class is also taken into consideration - Table VIII.4 -

children from large sibships in social class V had a relatively low (18%) prevalence of medical risk factors.

TABLE VIII.4

Medical risk factors in ESN/M children from sibships of 3 or less, or 4 or more in social class III, IV or V,

SOCIAL CLASS	Sibships 3 or less			Sibships 4 or more		
	Medical Risk			Medical Risk		
	Total	Factor (%)		Total	Factor (%)	
III	52	24	(46)	14	9	(64)
IV	26	11	(42)	16	6	(37)
V	30	12	(40)	22	4	(18)

SUMMARY OF FAMILY SIZE

1. Family size was significantly increased in study children. Families of 5 or more siblings were almost quadruple that expected from population norms.

2. Sibship size did not relate to the prevalence of medical risk factors.

3. Children from large families in social class V had the lowest prevalence of medical risk factors.

3. SIBSHIP POSITION

To calculate the 'expected' number of study children at each sibship position, the number of families with each size of sibship was divided by the number within the sibship. For example, of 26 families with a sibship of 4, one would expect 6.5 study children at each sibship position. The sum of the number expected at each position for each size of sibship, gave the total expected number.

i. Distribution

Shown in Table VIII.5

TABLE VIII.5

Place in sibship of 169 ESN/M children.

No. of Children in Family	No. of Families	Expected no. each position	Actual no. each position						
			1st	2nd	3rd	4th	5th	6th	7th or later
1	7	7	7						
2	75	37.5	38	37					
3	35	12	8	11	16				
4	26	6.5	4	6	6	10			
5	17	3.4	0	2	2	5	8		
6	7	1	0	1	2	2	0	2	
7	2	0.3	0	0	0	0	0	0	2
or later									
Total			57	57	26	17	8	2	2
Total EXPECTED NO.			67.7	60.7	23.2	11.2	4.7	1.3	0.3

Fifth-seven children (Table VIII.5) were born to primiparae. The expected number with equal distribution of sibship placing would be 67.7.

Twenty-nine children were fourth-or-later-born, as compared to 17.5 expected. Derived figures used in this analysis do not lend themselves to statistical analysis, but there was a minor shift in distribution of study children towards fourth-or-later born sibship position.

ii. Medical risk factors

This lack of any clearly defined relationship between sibship position and the attendance at ESN/M schools was reflected in the prevalence of associated medical features. Table VIII.6.

TABLE VIII.6

Medical risk factors and sibship position in 169 ESN/M children.

	SIBSHIP POSITION			
	1	2	3	4 or later
Number	57	57	26	29
Medical features (% in group)	25 (44)	18 (32)	13 (50)	15 (52)
Prenatal	5 (9)	3 (5)	6 (23)	8 (28)
Perinatal	17 (30)	12 (22)	5 (19)	7 (24)
Postnatal	3 (5)	3 (5)	2 (8)	0 (0)
No medical feature	32 (56)	39 (68)	13 (50)	14 (48)

Overall prevalence

The overall prevalence of medical features did not vary greatly in first -, second -, third -, fourth -, or later-born children.

Prenatal risk factors

Of 22 children with prenatal risk factors, 14 were third-or-later-born. Compared to first-or-second-born children, third-and-later-born appeared to be at increased risk of prenatal factors.

Three of the 8 children with familial chromosome abnormalities were born to mothers aged 38 years or over, and had 3 or 4 older siblings. The influence of advanced maternal age has already been discussed (Section V.1, f) in relation to chromosome abnormalities; this, and

not sibship position per se, carries over increased risk of chromosome abnormality associated with mental retardation in offspring.

Two of the 5 children with genetic syndromes - a girl [58] with Prader-Willi, and another [104] with Cohen syndrome, were fourth in their sibships. Their mothers were aged 28 years and 33 years respectively at the time of their births. Four of the 5 children with abnormalities of the CNS were third-or-later-born, but again, no mothers in this group were aged over 32 years. Advanced maternal age has an acknowledged association with an increased prevalence of non-chromosomal fetal abnormalities but was not a feature in these children. There is no known association between sibship position per se and non-chromosomal abnormalities, and, as numbers in this group are small no conclusions can be drawn.

Perinatal risk factors

These had been recorded more frequently in first-born than in subsequent children - of 41 children with perinatal problems, 17 were first-born. This, however, was not a significant finding - with 17 of 57 (30%) first-born children and 24 of 112 (21%) later-born children having perinatal problems.

$$(DF = 1: x^2 = 1.4; 0.50 > p > 0.10).$$

The prevalence of perinatal risk factors was not increased in fourth-or-later-born children.

Postnatal problems

The total number of children with mental retardation attributed to postnatal pathology was low (8) but none of the later-born children in large sibships had an adverse postnatal history. These few cases of postnatal problems did not provide any evidence that younger children in large sibships are at any increased risk of mental retardation arising from injury or CNS infection.

SUMMARY

1. First-born children were under-represented in the survey, with a minor shift in sibship positions towards fourth-or-later-born children.
2. The prevalence of medical risk factors was lowest in second-born children, but there was no significant relationship with sibship position.
3. Prenatal risk factors were most frequent in third-and-later-born children, but this may have been due, in part, to increased maternal age.
4. Perinatal risk features were more frequent in first-born children, but not significantly so. There was no increase in prevalence in children who were fourth-or-later-born.
5. No postnatal risk features were present in children who were fourth-or-later-born.

4. PARENTAL AGE

Parents' dates of birth were obtained at the home interview, hence age at the time of birth of the study children was known.

In 4 children [50, 62, 73, 109] born illegitimately, the father's age was not known.

Mean maternal age at birth of study child - 25.9yrs
SD 5.9
range 15-48 years.

Mean paternal age at birth of study child - 29.4yrs.
SD 5.9
range 18-56 years.

Parental ages were grouped in 5 year cohorts similar to those used in census reports. The Registrar General's report on parental age at birth (*HMSO, 1974*) gives the percentage in each age group. The percentage in each age group of parents of study children was calculated (from a total of 169 mothers, 165 fathers) and the distribution compared.

Maternal age at birth of study children corresponded precisely with that of the general population.

Three [40, 107, 133] mothers in the 35-39 age group had a child with a de novo chromosome translocation. (47, XX,+21; 47, XXY; 46, XX,15q-). In the over-40 age group, 3 children [5, 22, 94] born to mothers aged 41, 42, and 41 respectively, had normal karyotypes; the child [11] born to a 48 year old mother had Down syndrome.

TABLE VIII.7

Distribution of maternal age at birth of study children compared with that of the general population.

Maternal Age(yrs)	Study Population		General population (%)	Shift
	No.	(%)		
<20 years	23	13.6	13.6	-
20-24 years	50	29.6	29.6	-
25-29 years	64	37.8	37.8	-
30-34 years	13	7.7	7.7	-
35-39 years	15	8.9	8.9	-
>40 years	4	2.4	2.4	-
<hr/>				
Total	169	100.0	100.0	

Paternal age at birth of study children showed a minimal shift downwards compared with that of the general population. The proportion of fathers <20 years old - 2.4% - was similar, but 3.1% more study children than expected were born to fathers aged 20-34 years, and 3.1% less to fathers aged 35 years or more. This slight downward shift is of no apparent relevance; there was no evidence of increased paternal age being a factor in the aetiology of mild mental retardation.

TABLE VIII.8

Distribution of paternal age at birth of study children compared with that of the general population.

Paternal Age (yrs)	Study Population		General Population	Shift
	No.	(%)	(%)	
<20 years	4	2.4	2.4	-
20-24 years	30	18.2	17.2	+1.0
25-29 years	56	33.9	32.5	+1.4
30-34 years	48	29.1	28.4	+0.7
35-39 years	14	8.5	8.9	-0.4
>40 years	13	7.9	10.6	-2.7
<hr/>				
Total	165	100.0	100.0	

Population figures from *Birth Statistics - Office of Population Censuses and Surveys, HMSO, 1974.*

5. PARENTAL EDUCATION

This survey has not aimed to evaluate possible polygenic factors influencing innate intellectual ability; the aim has been to assess medical aetiological factors. The educational background of parents has been included for 2 reasons -

Firstly, as a rough - very rough - guide to a child's initial potential. This will, to some extent, affect the outcome of any given medical insult. A medical insult sufficient to lower the IQ by around 20 points - e.g. Klinefelter syndrome - could be sufficient to bring a child of low initial potential into the ESN/M range, but a child with Klinefelter syndrome whose initial potential was, say an IQ of 120, might well function adequately with an IQ around 100, in a normal school. *(Both boys in the survey with Klinefelter syndrome had parents of low educational ability.)*

Secondly, parents' levels of educational attainment provide an indication of the amount of intellectual stimulation likely to be provided at home. This again, could influence the long-term outcome of both the initial potential and of any given medical insult arising prenatally or in early childhood. Zellweger (1963) describes 2 children born to parents with IQs of 89-91, who had IQs of 68 and 73 respectively. The children were removed to good, stimulating home circumstances; their IQs rose to 105 and 113.

Thus medical pathology possibly associated with mental retardation has to be considered against the background of both initial intellectual capacity and of subsequent socio-cultural circumstances. It is with these considerations in mind that the levels of parental educational attainment have been studied in this section.

Method

The level of parental education was assessed at the home visit, from the account parents themselves gave of their education, and from their handling of the consent form. This form (*Appendix B*) was used for study children to be medically examined and tested at school. As parents were asked to read it and give a written signature of approval, it formed a useful guide to literacy.

Parents were allocated to one of four levels of educational attainment.

- Superior : education had continued to college or university level.
- Average : literate, no history of educational problems at school; regular school attendance; possibly, but not necessarily leaving school with a formal certificate of education.
- Low : semi-literate; attendance at normal school, but requiring special help.
- Very low : illiterate; attendance at ESN/M school.

Levels - "superior" and "very low" are reasonably clear-cut, but the distinction between "average" and "low" may be blurred. It is quite feasible that poor performers at normal school would not remember, after a gap of many years, receiving special help. However, without formal measurement of parental IQs - which was outwith the province of this study - any assessment of parental educational levels must be an approximate guide to mental ability.

A further problem was that for 38 children, it was not possible to see both parents. One child [62] lived with maternal grandparents, and neither parent was seen. Another child [101] was in care, but the mother was seen at home. Fathers of 3 boys had died. Parents of 33

children had divorced or separated, and of these, 30 parents - 27 fathers, 3 mothers - were not contacted. A further 3 fathers - all long-distance lorry-drivers - were not available at the home visit.

Reliance had, in cases where a parent was not seen, to be placed on second-hand information. In such cases a parent was graded "very low" only where there was a known history of ESN/M education. Where the parental occupation required literacy and the spouse was not aware of any educational problems, the parents were graded "average".

Table VIII.9 gives the educational assessment of this unseen group of parents. This information is included in **Table VIII.10** which gives details of parental education in relation to social class and the prevalence of medical risk factors.

TABLE VIII.9

Educational assessment of parents not seen personally.

EDUCATIONAL LEVEL (see text)	NEITHER PARENT SEEN	MOTHER NOT SEEN	FATHER NOT SEEN
Superior	-	-	-
Average	-	-	13
Low	-	1	12
Very low	1	2	9
Total	1	3	34

TABLE VIII.10

Parental education, social class and medical risk factors
in 169 ESN/M children.

PARENTAL EDUCATIONAL GRADING (see text)	SOCIAL CLASS					MEDICAL FEATURES
	II	III	IV	V	TOTAL	
Superior/superior	3	-	-	-	3	1
Superior/average	4	-	-	-	4	1
Average/average	2	43	10	-	55	30
Average/low	-	10	9	2	21	11
Low/low	-	7	11	21	39	10
Low/very low	-	3	11	15	29	12
Very low/very low	-	3	1	14	18	6
Total	9	66	42	52	169	71

Using the standards described above, parents of 115 children were assessed as having a level of education within the same 'grade' - superior, average, low or very low . In the remaining 54 children, parents' level of education fell within adjacent grades.

In 62 families both parents had achieved average or superior education; in 3 families both parents had received formal education over the age of 18 years.

There were 21 families in which one parent had educational problems. These had occurred in the mother alone in 11 of these families - and in the father alone in 10.

Both parents of 86 study children had had learning difficulties : in 18 of these families, both parents had attended ESN/M schools or were illiterate.

Parental educational attainment and social class (Table VIII.10)

Parents of children in social class II had an educational level which was average or above. Two-thirds of parents in social class III had both achieved average education, but 3 couples in this social class were graded "very low/very low". In these families the fathers had received ESN/M education and gone on to become drivers of heavy goods vehicles. The low level of attainment in these 3 couples and in parents of another 20 children from social class III may well have contributed to the need for ESN/M education by their children.

In social class IV, just under a quarter of the parents were "average/average". In half of this group neither parent had achieved average education, but there was only 1 couple where both were illiterate or had had ESN/M education.

In social class V there was "very low/very low" grading in parents of 14 of the 18 children.

Parental educational attainment and prevalence of medical risk factors
(Table VIII.10)

There were relatively few children in whom one or both parents had had higher education, but in only 2 of 7 such families were medical risk factors identified. The prevalence of medical risk factors was similar in children born to parents who were both illiterate, or had had ESN/M education, occurring in 6 out of 18 such children. However, looking at the groups more broadly, the prevalence of medical risk factors did appear to fall with the level of parental educational achievement. Of 83 children where at least one parent was of average educational attainment, medical risk factors were identified in 43 (57%). Where both parents had had learning difficulties, 28 out of 86 (33%) children had medical risk factors.

Pre-,peri-, and post-natal risk factors

The occurrence of these factors, in relation to parental educational attainment, is shown in Table VIII.11.

TABLE VIII.11

Parental education and pre-, peri-, and postnatal medical risk factors

PARENTAL EDUCATION (see text)	MEDICAL RISK FACTORS				Total
	Prenatal	Perinatal	Postnatal	None	
Grading					
Superior/superior	-	-	1	2	3
Superior/average	-	-	1	3	4
Average/average	11	13	6	25	55
Average/low	2	9	-	10	21
Low/low	1	9	-	29	39
Low/very low	6	6	-	17	29
Very low/very low	2	4	-	12	18
Total	22	41	8	98	169

There was no relationship between perinatal problems and parental educational attainment - 13 out of 55 (24%) children born to "average/average" parents had perinatal problems, compared with 4 out of 18 (22%) of children born to "very low/very low" parents.

All 8 children with postnatal risk factors had occurred in children in families where both parents had achieved average or superior educational attainment.

Parental educational attainment and prevalence of medical factors of possible significance.

There were 30 children with both parents of average or superior educational attainment who had no identifiable medical risk factors (Table VIII.12).

Nine of these children had no medical features in their histories. Medical features of possible significance occurring in the other 21 are shown in Table VIII.12.

TABLE VIII.12

Medical features of possible significance in 21 study children with no medical risk factors and both parents of average or superior education.

Prenatal features		9
Twinning	2	
Diabetes	1	
Hyperemesis	1	
Toxaemia	2	
Accident	2	
Operation and toxaemia	1	
Perinatal features		0
Postnatal features		1
Febrile fits	1	
Uncertain origin		11
Short stature	1	
3 or more dysmorphic features	3	
Behaviour disorder	2	
Epilepsy	1	
Short stature/dysmorphic features	1	
Dysmorphic features/epilepsy	1	
Dysmorphic features/behaviour disorder/ epilepsy	2	

COMMENT

When children were being recruited into the study, letters were sent to parents briefly explaining the study, suggesting a time for the home visit, and giving them an opportunity to participate. There was no response from 19 families, and no one at home at the time suggested for the home visit, or for a repeat visit - again with a time suggested by letter. These families were not included in the study. Omitting this group may well have biased the survey in favour of literate parents.

The allocation of parents to various levels of educational attainment can provide only a crude guide to their level of intelligence. Almost half the children in the survey had IQs >70, but were attending ESN/M schools. Moreover, the educational assessment of parents not seen personally is open to question. Literacy could not be assessed, and the grading "very low" was used only where a history of ESN/M education was known by the spouse. The grading of "average" on the basis of occupation is also debatable - 3 fathers with a history of ESN/M education were drivers of heavy goods vehicles. For these reasons no statistical analyses have been attempted.

1. Social Class

There was a crude correlation between the level of parental educational achievement and social class. All parents achieving high levels were in social class II; 43 out of 55 (55%) of parents with "average/average" education were in social class III; and 14 out of 18 (78%) parents of "very low/very low" grading were in social class V.

Although no parents of "low" education were in social class II, and no "average/average" couples were in social class V, in each social class differing levels of educational attainment were found.

In social class II, neither parent in 2 out of the 9 couples had received higher education.

In social class III, parental grading ranged from "average/average" to "very low/very low".

Social class does provide a guide, but an approximate guide only, to the family educational background - an impression also gained at the home visits.

ii. Educational attainment in couples

In no families did the educational attainment of both parents differ widely - couples were all within the same or adjacent "grades". It would seem a natural assumption that the tendency would be to select a partner of approximately the same educational background: and *Halperin (1947)* analysing the selection of partners, found that they were usually chosen from within the same range of intelligence.

iii. Sex of parent when only one had learning difficulties

There was no sex bias where just one parent had learning difficulties. *Cooper (1984)* suggested that a lower maternal IQ was more likely to lead to educational problems in children than a lower paternal IQ. In the present study, however, the mother alone had had learning problems in 11 families, the father alone in 10 families. The sex of the affected parent did not appear to influence referral for ESN/M education.

*iv. Medical risk factors**iv(a). Prenatal risk factors*

One would expect prenatal factors to be largely independent of parental education, and this was so. Eleven children with prenatal features were born to parents both of average education or above, and 11 to parents where one, or both, had low educational attainment.

iv(b). Perinatal risk factors

Women of low education might conceivably be less assiduous than their peers in seeking medical supervision in pregnancy, and hence possibly have an increased risk of perinatal problems. Perinatal problems, however, were, slightly less frequent in children born to mothers of low educational attainment. 22 out of 83 (26%) children with at least one parent of "average" education had perinatal problems : 19 out of 86 (22%) children where both parents were of "low" or "very low" education had perinatal risk factors.

iv(c). Postnatal risk factors

These had all occurred in children where both parents were of average education or above. As noted in relation to social class, study findings did not suggest that children with parents of low educational achievement are at increased risk of being retarded from medical features in their postnatal environment.

iv(d). Prevalence

It was somewhat surprising to find that the prevalence of medical risk factors was similar in children born to parents where at least one had

achieved higher education, to that in children where both parents were either illiterate, or had received ESN/M education.

Factors such as low initial potential, unstimulating home circumstances, could have contributed to the ESN/M education referral in the latter group, but were not apparent in the former group - do "unknown, unidentifiable" non-medical factors have a role in the aetiology of MMR equivalent to that of "poor socio-cultural" factors?

The numbers in both these groups of children, 7 and 18 respectively, were relatively small. Looking at the study group more widely, the prevalence of medical features was higher (51%) in 83 children who had at least one parent of average education or above, as compared to 33% in 86 children where both parents had had educational problems.

Where both parents were of average education or above -

- 30 children had no medical risk factors.

Where one or both parents were of low/very low education -

- 68 children had no medical risk factors.

These 68 study children, 40% of the total, form the core of MMR which has traditionally, been ascribed to polygenic socio-cultural influences in which medical factors have little, if any role.

V. MEDICAL FEATURES OF POSSIBLE SIGNIFICANCE

The 30 children with no identifiable medical or polygenic aetiology for their mental retardation, form 18% of the total number of study children. There was nothing abnormal in the histories of 9 of these children, and in a further 10 features of pre- or postnatal origin must be of very doubtful significance. The presence of physical and/or behavioural abnormalities in 11 other children is more likely to be related to their mental retardation, and does suggest especially

in the absence of any family history of retardation an unidentified aetiology common to both.

Emotional deprivation may have been a feature in some. This is considered in Section VIII,6.

SUMMARY

1. Both parents of 86 (51%) study children had had educational problems.
2. Social class provided an approximate guide only to parental educational attainment.
3. There were 68 (40%) study children with no medical risk features in whom both parents were of poor educational attainment.
4. There were 30 (18%) study children with no medical risk features, in whom both parents were of average education or above,

6. HOME ENVIRONMENT

The environment in which children live has great influence on their development. At one end of the scale there are appalling cases, such as that reported by *Koluchova (1972)* of twins who were kept isolated in a cellar. When found at the age of 7 years, they could not walk, could hardly speak, and were severely emotionally disturbed. Their IQs were about 40. They were subsequently adopted into a 'good' home. At the age of 20 years they had achieved normal social and emotional development, were in higher education, and had IQs of 115. At the other end of the scale are children whose parents devote their energies to educating them at home, and receive headlines when they achieve university placement at an early age. These are extremes, but illustrate how external factors play at least some part in a child's educational attainment.

A child from a disadvantaged home background, who receives scant attention or little encouragement to learn, is more likely to qualify for ESN/M education than a child with similar initial potential, who is valued and supported at home. *Masten (1988)* pointed out that parental warmth and family cohesion are beneficial to a child's school performance. Conversely, young children of depressed mothers showed developmental delay in a study by *Cox (1987)*.

Schiff (1978) studied pairs of siblings born into lower class families, in whom one sibling had been adopted at an early age into middle class families. In the home-reared children, 13 out of 20 had to repeat a grade or required special help at school, in the adopted children, 4 out of 32 had similar problems. In a follow-up study *Schiff (1982)* revealed a difference in IQs in the two groups. Three of the home-reared children had IQs <80, and just 7 had IQs >100. In the adopted children the lowest IQ was 81 and just 6 out of 32 had IQs <100.

Factors contributing to a 'good' or 'poor' home environment cannot be readily quantified. They were not studied in detail in this survey, where the prime aim was to consider the aetiology of medical genetic factors in MMR children; but home circumstances are particularly relevant in considering children referred to ESN/M schools, as opposed to those in ESN/S schools. It was felt that this aspect could not be ignored in the present study.

Method

At the home visit, parents were asked their opinion of

- the child's personality
- the child's educational development
- referral to ESN/M education

From this interview, a subjective impression was made of the child's emotional background at home. The school staff, from their relationship with parents, had also assessed the support provided by families. Information gained at the home visit was treated as confidential and not divulged to school staff, but when they volunteered information, this was in keeping with the author's assessment.

Parents were also asked at the home visit about their own medical histories, which included psychiatric treatment in some instances.

Results

Table VIII.13

Twenty-six study children were considered to have emotional deprivation. Their home circumstances are shown in Table VIII.13 which also shows the prevalence of other features in the various groups.

TABLE VIII.13

Home environment of 26 ESN/M children with emotional deprivation,
and associated factors.

			Parents of low educational grade	Medical features	No concomitant features
GROUP 1	Psychiatric illness in Mothers	6	3	3	0
GROUP 2	Inadequate single parent	10	10	2	0
GROUP 3	Domineering father/ stepfather, insupportive mother	6	5	1	1
GROUP 4	Lack of maternal support	4	0	0	4
Total		26	18	6	5

GROUP 1

Mothers of 6 children had a history of psychiatric illness. A brother and sister [46,47], and 3 other children [59, 106, 156] had mothers with depression who had attempted suicide in the last 2 or 3 years. One mother [35], a single parent, was under treatment for schizophrenia.

Three of these children had medical features which could be linked with their retardation, the other three had mothers who were barely literate.

GROUP 2

Eight children in the survey 9, 10 ,17, 72, 108, 112,113, 114] being cared for solely by their mothers, and two [98, 123] being cared for solely by their fathers, had depressed parents of low ability, who could scarcely cope and appeared apathetic towards their children.

Two children [9, 98] had medical features of significance in relation to their retardation; there were no medical risk factors in 8 of these children.

There were a further 9 children in whom the home environment appeared to be actively hostile

GROUP 3

In 5 children [4,18, 85, twins 81 and 82] the father, and in one child [86] the stepfather, was excessively domineering, distanced emotionally from the child, and prone to mete out punishment. In these families, the mother appeared subdued, and displayed little, if any, support for the child.

In five of these families parental educational attainment was low; they included one child with a low Apgar score at birth. The sixth child, whose behaviour bordered on autism, had parents who had both received higher education and no medical risk features.

GROUP 4

In four other families [36, 53, 95, 142] the mothers, all of normal intelligence, freely admitted to a complete lack of rapport with the child; one beat her child frequently. None of these children had medical features of probable aetiological significance.

Concomitant factors

Overall, a concomitant factor of low parental educational attainment, or medical pathology, or both, was present in 21 out of 26 children considered to have emotional deprivation.

Social Class

All social classes were represented in this group of children considered to have emotional deprivation. Table VIII.14.

Homes of children in the first 3 groups were disorganised and ill-kept, irrespective of social class.

Mothers who expressed hostility to their children kept their house in good order; the children were not physically deprived. Three of the four, however, were small, with height at or below the 3rd centile.

TABLE VIII. 14

Social class of children with emotional deprivation.

Social Class		II	III	IV	V
GROUP 1	Psychiatric illness in mothers	-	5	1	-
GROUP 2	Inadequate single parent	-	1	2	7
GROUP 3	Domineering father/ stepfather, insupportive mother	1	-	2	3
GROUP 4	Lack of maternal support	-	3	1	-
Total		1	9	6	10

COMMENT

Any assessment of quality of parental care found at a single home interview must be interpreted with caution, but the subjective impression was that these 26 children received little, if any, support at home. This impression was not dependent on physical home circumstances - many children in poor home conditions were felt to be well cared for emotionally; conversely, 4 children living in good home conditions were felt to be emotionally deprived.

In the first 2 groups - mothers with mental illness, and apathetic single parents, parental attitudes to study children and their siblings were similar. The negative attitudes expressed were not felt to result from the child's retardation, but from the parent's own circumstances.

The 6 children who had domineering fathers appeared to have become the main targets for the father's aggression - their siblings were more favoured, and the study children were isolated within their families. This situation was long-standing and had not arisen as a result of ESN/M referral, but may well have contributed to it.

Parents whose child fails to live up to their academic expectations may react by increasing emotional and intellectual support, or they may regard the child as 'stupid' and become resentful. Thus the child's retardation - and the subsequent emotional atmosphere would do nothing to help the child.

The same may be true of the mothers who expressed hostility - although one mother expressed a complete "lack of bonding" from the child's birth.

Whatever the cause, the lack of emotional support given to these children may well have contributed to their ESN/M referral, but is not a feature which can be quantified.

SUMMARY

1. Assessment of emotional deprivation was subjective, and made at a single home interview.
2. Twenty-six out of 169 (15.4%) study children were considered to have emotional deprivation.
3. In 21 of these 26 children, there was a concomitant factor, of medical pathology or low parental educational attainment, which could have contributed to ESN/M referral.
4. Five children had no concomitant factor. They all had what amounted to parental rejection - 4 by their mothers, 1 by his father.
5. In all 26 children, although it cannot be quantified, emotional deprivation may well have contributed to ESN/M referral.

CONCLUSIONS

1. Medical risk factors were identified in 71 (42%) of this group of children with mild mental retardation. Whilst most of these factors were fortuitous, the presence of identified aetiology in just under half of the study children offers potential - even if at present largely theoretical - for reduction in the prevalence of mild mental retardation.

2. There were 19 (11.2%) study children with genetic/part-genetic conditions which had probably contributed directly to their retardation. The sporadic or varied nature of these conditions was such that effective genetic counselling would not be feasible.

Results of this survey therefore suggest that while recognised genetic causes contribute to mild mental retardation, the scope for reduction in the prevalence of mild mental retardation by genetic counselling is limited.

3. Chromosome abnormalities were present in 9 (5%) children : 6 of these were detected during the survey. As chromosome abnormalities were detected in children with no dysmorphic features I would recommend that consideration be given to karyotyping all children referred for ESN/M education.

No cases of fragile-X syndrome were found in this survey, but results of other studies indicate that chromosome analysis should include looking specifically for the fragile-X chromosome. (Very recent research suggests that this may be replaced by gene probe analysis.)

4. Three children had genetic syndromes diagnosed in the course of the survey. I would recommend that school medical officers, when examining children in ESN/M schools, look carefully for 'soft'

dysmorphic signs. Any child with 3 or more minor dysmorphic features should be referred to a paediatrician or geneticist.

5. One child had alcohol fetopathy, identified during the survey. In this relatively small study maternal alcoholism was not a major contributor to mild mental retardation, in contrast to findings in Sweden and the USA.

6. Screening of children and their mothers for biochemical defects revealed no abnormalities. Routine biochemical screening of children with mild mental retardation is unlikely to be worthwhile, but should be considered if there are suggestive signs.

Although no cases of undiagnosed maternal phenylketonuria were found, this should be kept in mind when there is no evident cause for a child's retardation.

7. Perinatal stress had occurred in 46 (27%) children, and was the sole risk factor in 41. Although any definitive link between perinatal stress and mental retardation is difficult to confirm, this prevalence does suggest that perinatal pathology has a role in the aetiology of mild mental retardation.

8. Postnatal medical factors were linked to the presence of mild mental retardation in 8 (4.7%) children. They found a relatively small, but definitive, aetiological group.

9. Abnormal medical features, of no proven association with mild mental retardation, were present in a further 63 (37%) children. Although no firm conclusions could be drawn from this group, certain points emerged.

Maternal diabetes was the sole medical factor in 3 children : children born to diabetic mothers are at an increased risk of physical

abnormalities, but there is no reported association with mental retardation. One of these children, with parents of normal intelligence, had a brother who was also retarded. These numbers are small, but raise the possibility of neurological deficit in children born to diabetic mothers.

Small stature was a prominent feature, occurring in 30 (18%) children. Impairment of physical and mental development may occur together.

Incoordination, which featured in 42 (25%) children may also be an outward sign of impaired mental development.

10. There was a history of learning difficulties in one or both parents of 107 (63%) children. Non-specific hereditary factors undoubtedly contribute to the prevalence of mild mental retardation. However, over one third of study children had no familial background of learning problems, and the cause of their retardation must lie elsewhere.

11. A group of 25 (15%) children had no medical risk factors identified, and no history of parental learning difficulties. The cause of their retardation remains obscure.

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APPENDIX A

APPENDIX A

This appendix records case histories and photographs of children in the survey.

Photographs were not available for 8 children. Copies of official school photographs were used from Forest Edge School, and of these, 6 children had been absent on the appropriate day. Two other mothers did not wish their child's photograph to be used in the study. None of these children were considered dysmorphic.

Apgar scores, available for 116 children (Table V.8), have been given only when a score of less than 7 had been recorded at 5 minutes.

Home circumstances are mentioned only when they were considered to be poor at the home visit (*Section VIII.6*).

As in the main text, features of probable aetiological significance are underlined.

APPENDIX A**CASE REPORTS****Case 1****Male****IQ 66**

Seen aged 8 years.

Mother aged 25 years, father 33 years, at birth. Younger of two male siblings. Social class III - father - car-mechanic. Normal pregnancy and labour : gestation 42 weeks. BW 3316 gm. Sudden onset of haemophilus meningitis aged 9 weeks. Prurulent subdural L.sided effusion. Grand mal epilepsy till 18 months old. Aggressive behaviour until 4 years old, with self-biting. Persistence of antisocial behaviour. [DSM 312.10]. Incoordination - R.sided.

Medical known risk factors - haemophilus meningitis
 other factors - incoordination
 - epilepsy
 - behaviour disorder

Familial retardation

- none.

Case 2**Male****IQ 81**

Seen aged 8 years.

Mother aged 20 years, father 21 years, at birth. One female sibling. Social class III - father - electrician. Mild hydramnios. Gestation 40 weeks. Delivered in G.P. unit : prolonged labour. BW 2920 gm. Blue and limp for 3 hrs. after birth. No motor or speech delay. No incoordination.

Medical known risk factors - neonatal cyanosis
 other factors - none

Familial retardation

- none.

Case 3**Female****IQ 69**

Seen aged 7 years.

Mother aged 21 years, father 30 years, at birth. Younger of 2 female siblings. Social class V - father - unemployed labourer. Normal pregnancy and labour. Gestation 36 weeks. BW 2280 gm. Grey turns and vomiting in first week of life. No motor or speech delay. No incoordination. Height below 3rd centile. (Both parents 5ft tall.)

Medical known risk factors - neonatal cyanosis
 other factors - small stature

Familial retardation

- father illiterate.

Case 4**Male****IQ not tested**

Seen aged 5 years.

Mother aged 36 years, father 27 years, at birth. One younger sibling - female. Social class II - father - pharmacist. Normal pregnancy. Elective Caesarean section for placenta praevia at 40 weeks gestation. No motor delay : speaking at 2 years, then regressed, hospital investigation at 3 years for slow development and lack of speech. Nil found. Autistic features. Coordination - not tested. Height on 3rd centile.

Medical	known risk factors	- none
	other factors	- small stature
		- behaviour problem [DSM 299.00]
Familial retardation		none
Poor home circumstances		- domineering father
		- unsupportive mother.

Case 5 **Female** **IQ 72**

Seen aged 10 years.

Mother aged 41 years, father 43 years, at birth. Youngest of 5 siblings - 3 boys, 2 girls. Social class V - father - unemployed labourer. Normal pregnancy and labour. BW 3540 gm at 40 weeks' gestation. No motor or speech delay. No incoordination. Obese, anti mongoloid slope to eyes.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- father illiterate
		- 1 brother ESN/M.

Case 6 **Male** **IQ 86**

Seen aged 10 years.

Mother aged 29 years, father 34 years, at birth. Mother - grand mal epilepsy in teens. On epanutin and phenobarbitone from 14-20 years. Younger of 2 male siblings. Social class II - father - planning engineer. Normal pregnancy and labour. BW 3685 gm at 40 weeks' gestation. Positional bilateral talipes at birth - corrected with physiotherapy. Kyphosis and scoliosis noted at 1 year. Not treated. Motor and speech delay. Emotional lability. Macrocephaly. **Dysmorphic features**- prominent metopic sutures, prominent nasal tip, prominent antihelices

both ears, high arched palate, asymmetric thorax, some incoordination.

Medical	known risk factors	- none
	other factors	- Macrocephaly
		- >3 dysmorphic features
		- behavioural disturbance [DSM 312.10]
		- incoordination
Familial retardation		- none.

Case 7 **Male** **IQ 69**

Seen aged 7 years.

Mother aged 20 years, father 33 years, at birth. Only child. Social class III - father - theatre technician. Normal pregnancy and labour. Gestation 42 weeks. BW 3146 gm. Noted to be dysmorphic at birth. **Chromosomes** - 46, XY, dup.(14) (q21-q22) - father 46,XY: mother 46,XX. Born in G.P. unit : transferred to main hospital at 5 days because of jaundice - received phototherapy. Hirschsprung's disease - colostomy at 14 months, resection at 18 months. Mild motor and speech delay - received speech therapy. **Dysmorphic features**- trigonocephaly, bilateral epicanthic folds, microphthalmos, long flat philtrum, high arched palate, short broad thumbs, L.Simian crease, tight Achilles tendon, R and L., mild incoordination.

Medical	known risk factors	-chromosome abnormality
	other factors	- neonatal jaundice

Familial retardation

- incoordination
- >3 dysmorphic features
- none.

Case 8

Male

IQ 87

Seen aged 11 years.

Mother and father both aged 20 years, at birth. Second of 4 siblings, 3 boys, 1 girl. Social class V - father - farm worker. Maternal toxemia in pregnancy. Normal labour. BW 2806 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical

known risk factors
other factors

- none
- toxemia

Familial retardation

- father and six of 9 paternal uncles illiterate
- 2 male siblings ESN/M
- mother semi-literate

Case 9

Male

IQ 85

Seen aged 6 years.

Mother and father both aged 29 years, at birth. Younger of 2 male siblings - brother of [10]. Social class IV - father - factory packer. Normal pregnancy. Meconium stained liquor at birth, low forceps delivery. BW 3300 gm at 40 weeks' gestation. Started grunting 10 minutes after birth, cyanotic turns. In SCBU for 10 days. Ventricular septal defect - repaired at 2 years of age : hospital admission at 7 months because of failure to thrive. No motor delay : speech slow - received speech therapy. No incoordination.

Medical

known risk factors
other factors

- neonatal cyanosis
- VSD

Familial retardation

- both parents semi-literate
- brother also ESN/M

Poor home circumstances

- apathetic single mother.

Case 10

Male

IQ 76

Seen aged 9 years.

Mother and father both aged 25 years, at birth. Older of 2 male siblings - brother of [9]. Social class IV - father - factory packer. Normal pregnancy and labour. Gestation 41 weeks. BW 3420 gm. No motor delay : speech slow - received speech therapy. No incoordination.

Medical

known risk factors
other factors

- none
- none

Familial retardation

- both parents semi-literate
- brother also ESN/M.

Poor home circumstances

- apathetic single mother.

Case 11**Male****IQ 83**

Seen aged 11 years.

Mother aged 35 years, father 31 years, at birth. Second youngest of 4 siblings, all male. Social class III - father - bus driver. Normal pregnancy. Breech delivery at 40 weeks' gestation : prolapsed cord, with forceps to the after-coming head. Collapsed at birth - Apgar 6 at 5 mins. BW 2610 gm. In incubator for first week of life. No motor delay : speech delayed - had speech therapy. Coordination impaired.

Medical known risk factors - low Apgar score
 other factors - incoordination
Familial retardation - none

Case 12**Male****IQ 68**

Seen aged 9 years.

Mother aged 27 years, father aged 32 years, at birth. Youngest of 3 siblings, 2 male, 1 female. Social class V - father - labourer. Normal pregnancy and labour - home delivery. BW 4053 gm at 40 weeks' gestation. No motor delay : speech delayed - received speech therapy. Grand mal epilepsy from the age of 8 years. On sodium valproate. Aggressive behaviour. Some incoordination.

Medical known risk factors - none
 other factors - epilepsy
 - behaviour problems [DSM 312.10]
 - incoordination
Familial retardation - none.

Case 13**Female****IQ 78**

Seen aged 8 years.

Mother aged 20 years, father aged 22 years, at birth. Younger of 2 female siblings. Social class V - father - labourer. Normal pregnancy and labour. BW 3912 gm at 40 weeks' gestation. No motor or speech delay. Height <3rd centile. No incoordination.

Medical known risk factors - none
 other factors - small stature
Familial retardation - father illiterate.

Case 14**Male****IQ 83**

Seen aged 8 years.

Mother and father both aged 30 years, at birth. Younger of 2 male siblings. Social class II - father - business director. Bleeding in pregnancy at 6 and 10 weeks' gestation. No early motor or speech delay. Pertussis aged 2 years - severely ill for 3 months. Development delayed thereafter - bone age of 2.8 years at 3.5 years; of 4.5 years at 6.5 years. No incoordination.

Medical known risk factors - severe pertussis
 other factors - threatened abortion
 - small stature
Familial retardation - none.

Case 15**Female****IQ 83**

Seen aged 7 years.

Mother and father both aged 26 years, at birth. One sibling - older brother. Social class III - father - plumber. Hyperemesis in pregnancy with Debendox taken throughout. No problems in labour. No motor or speech delay. No incoordination.

Medical

known risk factors - none
other factors - hyperemesis
- Debendox

Familial retardation

- none.

Case 16**Male****IQ 74**

Seen aged 9 years.

Mother aged 24 years, father aged 27 years, at birth. youngest of 5 siblings, 3 girls, 2 boys. Social class V - father - labourer. Mother severely anaemic in pregnancy. Normal delivery at 40 weeks' gestation. BW 2290 gm - <3rd centile. Weight loss in 1st week - fell to 2000 gm. In SCBU for 10 days. Motor and speech delay. Incoordination.

Medical

known risk factors - none
other factors - maternal anaemia in pregnancy
- small for gestational age
- neonatal weight loss
- incoordination

Familial retardation

- both parents semi-literate
- one brother, one sister ESN/M.

Case 17**Male****IQ 72**

Seen aged 10 years.

Mother aged 19 years, father aged 21 years, at birth. Younger of 2 male siblings. Social class V - father - labourer. Normal pregnancy and labour. BW 4110 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical

known risk factors - none
other factors - none

Familial retardation

- both parents illiterate
- brother also ESN/M.

Poor home circumstances

- inadequate and apathetic single mother.

Case 18**Male****IQ 61**

Seen aged 5 years.

Mother aged 23 years, father aged 28 years, at birth. Youngest of 3 siblings, 2 boys, 1 girl. Social class IV - father - van driver. Ante-partum haemorrhage 24 hours before delivery at 33 weeks' gestation. BW 2324 gm. Incubated for 48 hours. No motor delay : speech - apparently normal at 18 months, then regressed : has had speech problems since with speech therapy. No incoordination.

Medical

known risk factors - none
other factors - ante-partum haemorrhage
- prematurity

Familial retardation
 Poor home circumstances

- father semi-literate
- aggressive and domineering father,
- unsupportive mother.

Case 19

Female

IQ 64

Seen aged 10 years.

Mother aged 19 years, father aged 26 years, at birth. One sibling, a monovular twin - [20]. Social class III - father - HGV driver. Twin pregnancy : Kielland's forceps delivery (2nd twin) at gestation of 39 weeks. BW 2267 gm - <3rd centile. In SCBU for 3 days. No motor or speech delay. No incoordination.

Medical

known risk factors

- none

other factors

- twin
- small for gestational age

Familial retardation

- twin sister ESN/H.

Case 20

Female

IQ 72

Seen aged 10 years.

Mother aged 19 years, father aged 26 years, at birth. One sibling - monovular twin - [19]. Social class III - father - HGV driver. Twin pregnancy : breech extraction (1st twin) at gestation of 39 weeks. BW 2409 gm - on 3rd centile. In SCBU for 3 days. No motor or speech delay. No incoordination.

Medical

known risk factors

- none

other factors

- twin
- small for gestational age

Familial retardation

- twin sister ESN/H.

Case 21

Male

IQ 68

Seen aged 8 years.

Mother aged 25 years, father aged 27 years, at birth. Fourth of 5 siblings, 4 boys, 1 girl. Social class IV - father - factory worker. Normal pregnancy and labour. BW 3061 gm at 40 weeks' gestation. Motor and speech delay - required speech therapy. Febrile fits aged 2 and 3 years. **Dysmorphic features** - shield chest, bilateral clinodactyly. Attention-seeking behaviour. Marked incoordination. **Chromosomes** - 48, XXYY.

Medical

known risk factors

- chromosome abnormality

other factors

- febrile fits
- behaviour disorder [DSM 312.10]
- incoordination

Familial retardation

- none.

Case 22

Male

IQ 78

Seen aged 11 years.

Mother aged 42 years, father aged 48 years, at birth. Five older half-siblings - 3 girls, 2 boys. No full siblings. Social class V - father (dead) - labourer. Toxaemia, with hypertension for 3 weeks prior to normal delivery at 39 weeks' gestation. BW 2838 gm. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- toxemia
Familial retardation		- father ESN/M, as were his 8 siblings.
		- 1 brother ESN/M
		- [50] - paternal cousin.

Case 23**Male****IQ 73**

Seen aged 5 years.

Mother aged 28 years, father 32 years, at birth. Younger of 2 male siblings. Social class III - father - metal worker. Toxaemia in pregnancy. Caesarean section at 38 weeks' gestation for unstable lie. Apgar score at birth 2, but 8 at 5 minutes. Neonatal cyanotic episodes on days 1, 2 and 3. At age 11 months, diagnosed as having mild cerebral palsy, with R. hemiparesis. Partial palsy of 3rd cranial nerve, with R. ptosis. Motor and speech delay. Diminished power R. side : tight R. Achilles tendon. Poor coordination.

Medical	known risk factors	- neonatal cyanosis
	other factors	- toxemia
		- incoordination
Familial retardation		- none.

Case 24**Male****IQ 76**

Seen aged 11 years.

Mother aged 19 years, father aged 21 years, at birth. Third of 6 siblings, 4 boys, 2 girls. Social class V - father - labourer. Normal pregnancy and labour. BW 2893 gm at 40 weeks' gestation. No motor or speech delay. No incoordination. Height below 3rd centile.

Medical	known risk factors	- none
	other factors	- small stature
Familial retardation		- strong history. Both parents illiterate, 2 brothers ESN/M.

Case 25**Female****IQ 75**

Seen aged 7 years.

Mother aged 25 years, father aged 31 years, at birth. Younger of two female siblings. Social class IV - father - plant attendant. Normal pregnancy and labour. BW 2665 gm at 41 weeks' gestation - on 3rd centile. Slight motor and speech delay. Poor coordination. Height on 3rd centile.

Medical	known risk factors	- none
	other factors	- small stature
		- incoordination
Familial retardation		- none.

Case 26**Female****IQ not tested**

Seen aged 7 years.

Mother aged 28 years, father aged 30 years, at birth. Social class III - father - driving instructor. Toxaemia in pregnancy: spontaneous normal delivery at 38 weeks' gestation. BW 3345 gm. No motor delay. Started vocalising at 11 months, then stopped. Tongue-tie released aged 5 years. Features of autism with strong resistance to anything new or out of routine; hyperactive. Rapid unintelligible speech. Coordination could not be tested.

Medical

known risk factors - none
 other factors - behaviour disorder [DSM 299.00]
 - toxaemia

Familial retardation

- none.

Case 27**Female****IQ 61**

Seen aged 11 years.

Mother aged 20 years, father aged 26 years, at birth. One of 5 siblings: 2 boys, 3 girls. Twin of [28]. Social class IV - father - operator at power station. Mother anaemic in pregnancy. First twin to be born. Normal delivery at 36 weeks' gestation. BW 2430 gm. Early motor, but no speech, delay. No incoordination.

Medical

known risk factors - none
 other factors - twin
 - anaemia in pregnancy
 - premature delivery

Familial retardation

- twin and older sister ESN/M.

Case 28**Female****IQ 52**

Seen aged 11 years.

Mother aged 20 years, father aged 26 years, at birth. One of 5 siblings: 2 boys, 3 girls. Twin of [27]. Social class IV - father - operator at power station. Mother anaemic in pregnancy. Second twin to be born, at 36 weeks' gestation - breech, delivered spontaneously. BW 2500 gm. Early motor, but no speech, delay. No incoordination.

Medical

known risk factors - none
 other factors - twin
 - anaemia in pregnancy
 - prenatal delivery

Familial retardation

- twin and older sister ESN/M.

Case 29**Female****IQ 71**

Seen aged 9 years.

Mother aged 28 years, father aged 29 years, at birth. Youngest of 3 female siblings. Social class III - father - HGV driver. Normal pregnancy and labour. BW 3450 gm at 38 weeks' gestation. No motor or speech delay. No incoordination.

Medical known risk factors - none
 other factors - none
 Familial retardation - none.

Case 30**Female****IQ 66**

Seen aged 9 years.

Mother and father both aged 25 years, at birth. One younger brother. Social class IV - father - panel beater. Normal pregnancy and labour. BW 2891 gm at 40 weeks' gestation. No motor or speech delay, no incoordination.

Medical known risk factors - none
 other factors - none
 Familial retardation - none.

Case 31**Male****IQ 60**

Seen aged 10 years.

Mother aged 25 years, father aged 30 years, at birth. One younger sister. Social class III - father - process coordinator at power station. Hyperemesis in pregnancy. Cord round neck at birth at 42 weeks' gestation - Apgar score of 4 at 5 minutes. BW 3798 gm. Motor and speech delay. Hospital investigation aged 9 years - when EEG showed "an excess of beta activity. Usual spatial and temporal distribution of rhythms has not developed. This could reflect cortical damage from an anoxic episode." Thyroid, hepatic and renal function all normal. Incoordination, clumsy child.

Medical known risk factors - low Apgar score
 other factors - hyperemesis
 - abnormal EEG
 - incoordination
 Familial retardation - none.

Case 32**Male****IQ 70**

Seen aged 11 years.

Mother aged 26 years, father aged 21 years, at birth. Eldest of 3 siblings: 2 boys, 1 girl. Social class V - father - delivery man. Normal pregnancy and labour. BW 3061 gm at 40 weeks' gestation. No motor or speech delay. Mild incoordination.

Medical known risk factors - none
 other factors - macrocephaly
 - incoordination
 Familial retardation - both parents semi-literate, 1 brother ESN/M.

Case 33

Male

IQ 79

Seen aged 9 years.

Mother aged 27 years, father aged 39 years, at birth. Youngest of 3 siblings: 2 boys, 1 girl. Social class III - father - steeplejack. Hyperemesis in pregnancy. Normal delivery at 40 weeks' gestation. BW 3340 gm. No motor or speech delay. No incoordination.

Medical

known risk factors

- none

other factors

- hyperemesis

Familial retardation

- sister ESN/H

- brother - behavioural disturbance, in psychiatric unit.

Case 34

Male

IQ 58

Seen aged 9 years.

Mother aged 27 years, father aged 29 years, at birth. Younger of 2 male siblings. Social class IV - father - van-driver. Normal pregnancy and labour. BW 2806 gm at 40 weeks' gestation. No motor or speech delay. Febrile fits (2) aged 2 and 3 years. No incoordination.

Medical

known risk factors

- none

other factors

- febrile fits

- macrocephaly

Familial retardation

- none.

Case 35

Female

IQ 74

Seen aged 9 years.

Mother aged 22 years, father aged 28 years, at birth. Mother - long-standing schizophrenia. Younger of 2 female siblings. Social class III - father - lance-corporal in army. Heavy intake of alcohol throughout pregnancy. Threatened abortion at 16 weeks. Normal delivery, BW 2353 gm at 37 weeks' gestation. Hypotonic at birth: tube fed for 3 weeks. No motor delay; speech delayed until 4 years old. Febrile fits at 9 and 10 months old. Mild microphthalmos. No incoordination.

Chromosomes

- 46,X,t(X;19) (p11.2:p13.3)

- de novo translocation

Medical

known risk factors

- chromosome abnormality

other factors

- alcohol in pregnancy

- threatened abortion

- febrile fits

Familial retardation

- none.

Poor home circumstances

- single mother with erratic behaviour, on depixol for schizophrenia

Case 36**Male****IQ 51**

Seen aged 9 years.

Mother aged 21 years, father aged 32 years, at birth. One younger sister. Social class III - father - electronics engineer. Normal pregnancy and labour. BW 2834 gm at 41 weeks' gestation. No motor delay. Speech delayed - hospital investigation for lack of speech at 3 years. Bone age, skull x-ray, blood film, EEG and chromosomes all normal. Brachycephaly, synophrys, triangular face, large prominent ears, high palate. No incoordination.

Medical

known risk factors - none
other factors - >3 dysmorphic features

Familial retardation

- none

Poor home circumstances

- lack of maternal rapport.

Case 37**Female****IQ 72**

Seen aged 8 years.

Mother aged 22 years, father aged 27 years, at birth. Second of 3 female siblings. Social class V - father - labourer. Normal pregnancy and labour. BW 3005 gm at 40 weeks' gestation. No motor or speech delay. Height <3rd centile. No incoordination.

Medical

known risk factors - none
other factors - short stature

Familial retardation

- father and mother illiterate
- 1 sister ESN/M.

Case 38**Female****IQ 67**

Seen aged 9 years.

Mother aged 39 years, father aged 47 years, at birth. Three older half-siblings: 2 boys, 1 girl; 1 older male full-sibling. Social class III - father - builder. Hyperemesis in pregnancy. Normal delivery at 41 weeks' gestation. BW 2608 gm (<10thcentile). Mild motor delay; speech delayed until 5 years old. No incoordination. Speech still very poor. Facies suggestive of Down syndrome. Misplaced incisors, poor teeth. Ichthiosis.

Medical

known risk factors - none
other factors - >3 dysmorphic features
- hyperemesis

Familial retardation

- none.

Case 39**Male****IQ 71**

Seen aged 10 years.

Mother aged 18 years, father aged 19 years, at birth. One younger sister. Social class V - father - labourer. Normal pregnancy and labour. BW 2570 gm at 38 weeks' gestation. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- both parents semi-literate.

Case 40**Male****IQ 76**

Seen aged 8 years.

Mother aged 38 years, father aged 46 years, at birth. Youngest of 3 male siblings. Social class IV - father - bakery worker. Toxaemia in pregnancy; placental insufficiency. Normal delivery at 36 weeks' gestation. BW 2182 gm (<10th centile). Collapsed at birth - Apgar score 5 at 5 minutes. No motor delay. Speaking at 15 months, then regressed. Speech still poor when seen. Incoordination - only in hand-tapping.

Chromosomes

- 47,XXY.

Medical

known risk factors

- Klinefelter syndrome

other factors

- low Apgar score

- toxaemia

- prematurity

Familial retardation

- mother - borderline ESN/M

Case 41**Male****IQ not tested**

Seen aged 6 years.

Mother aged 29 years, father aged 30 years, at birth. Father epileptic - on phenytoin. One younger sister. Social class V - father - farm worker. Persistent hypertension in pregnancy. Low forceps delivery at 33 weeks' gestation. BW 1800 gm. Neonatal cyanosis; hyaline membrane disease. Jaundice - treated with phototherapy. Febrile fits (2) aged 14 months - treated with phenobarbitone. Mild motor and speech delay. Head large in proportion to body size: hypertelorism. clumsy gait, with incoordination.

Medical

known risk factors

- neonatal cyanosis

other factors

- toxaemia

- prematurity

- febrile fits

- odd appearance

- incoordination

Familial retardation

- father illiterate

- mother semi-literate.

Case 42**Female****IQ 79**

Seen aged 10 years.

Mother aged 19 years, father aged 21 years, at birth. One younger brother with Werdnig-Hoffmann disease. Social class IV - father - despatch clerk. Mother on Ovaran 40 for first 16 weeks' gestation. Toxaemia. Normal delivery at 39 weeks' gestation. BW 2551 gm. No motor delay; speech mildly delayed. Long face with

bilateral epicanthic folds. No incoordination.

Medical	known risk factors	- none
	other factors	- hormone medication in pregnancy
		- toxæmia
Familial	retardation	- none.

Case 43	Male Seen aged 6 years.	IQ Not tested
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Mother aged 18 years, father aged 20 years, at birth. Eldest of 4 siblings: 3 boys, 1 girl. Social class III - father - master butcher. Normal pregnancy. Labour - fetal brachycardia, high forceps delivery at 41 weeks' gestation. BW 2150 gm (<3rd centile). Bilateral cleft lip and palate. Poland's anomaly, with absent L.pectoralis major, and L.hand <R. Partial syndactyly L.hand. Mild motor and speech delay. Some incoordination.

Medical	known risk factors	- fetal distress
	other factors	- small for gestational age
		- major malformations
Familial retardation		- none

Case 44 Male IQ 84
Seen aged 9 years.

Mother aged 28 years, father aged 32 years, at birth. Second of 3 siblings: 1 boy, 2 girls. Social class III - father - HGV driver. Normal pregnancy and labour. BW 3118 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial	retardation	- mother and 2 of her sisters ESN/M.

Case 45 Female IQ 76
Seen aged 9 years.

Mother aged 23 years, father aged 24 years, at birth. One older sister. Social class V - father - labourer. Normal pregnancy and labour. BW 2920 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- both parents ESN/M
		- sister ESN/M.

Case 46**Female****IQ 70**

Seen aged 10 years.

Mother aged 22 years, father aged 39 years, at birth. Second of 3 siblings: 2 girls, 1 boy; sister of [47]. Social class III - father - railway signalman (unemployed). Normal pregnancy and labour. BW 3005 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical

known risk factors - none
other factors - none

Familial retardation

- mother semi-literate
- 1 brother [47] ESN/H.

Poor home environment

- mother depressed, suicidal.

Case 47**Male****IQ 51**

Seen aged 8 years.

Mother aged 24 years, father aged 41 years, at birth. Youngest of 3 siblings: 2 girls, 1 boy; brother of [46]. Social class III - father - railway signalman (unemployed). Normal pregnancy and labour. BW 3401 gm at 40 weeks' gestation. Mild motor and speech delay. Incoordination, in all tests except hopping.

Medical

known risk factors - none
other factors - incoordination

Familial retardation

- mother semi-literate
- 1 sister [46] ESN/H

Poor home environment

- mother depressed, suicidal.

Case 48**Male****IQ 70**

Seen aged 8 years.

Mother and father aged 30 years, at birth. Younger of 2 male siblings. Social class III - father - sheet metal worker. Normal pregnancy and labour. BW 4309 gm at 40 weeks' gestation. Twitching noted in first week of life. No motor delay. Comprehension and speech slow - spoke at 3 years. Poor grasp of language. Grand mal fits at 3 years, 4 years and 4 years, occasionally since. On sodium valproate. EEG at age 5 years - "epileptiform activity". Poor coordination.

Medical

known risk factors - neonatal twitching
other factors - epilepsy

Familial retardation

- incoordination
- none.

Case 49**Female****IQ 60**

Seen aged 8 years.

Mother aged 26 years, father aged 27 years, at birth. One younger brother. Social class II - father - transport manager. Normal pregnancy and delivery. BW 4592 gm at 40 weeks' gestation - >97th centile. No early motor or speech delay. Non-accidental head injury at 15 months. Readmitted one month later with convulsions. Bilateral subdural haematomata and retinal/macular haemorrhages. L-sided weakness

persisted following removal of blood clots; poor peripheral vision. Perceptual problems, with difficulty in distinguishing shapes, and poor visual coordination. Limited movement of L. arm and leg; coordination impaired. Appearance suggestive of Sotos syndrome - long face, narrow palate, extra crease on digits 1-4, long hands and feet.

Medical known risk factors - intracranial haemorrhage
other factors - > 3 dysmorphic features
Familial retardation - *none.*

Case 50**Female****IQ 72**

Seen aged 8 years.

Mother aged 18 years, at birth: no details of father known. No full siblings; 3 younger half-siblings: 2 girls, 1 boy. Social class V - stepfather - labourer (unemployed). Normal pregnancy and labour. BW 3401 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical known risk factors - none
other factors - none
Familial retardation - *mother semi-literate*
- *[22] - maternal cousin.*

Case 51**Female****IQ 70**

Seen aged 8 years.

Mother and father both aged 19 years, at birth. Second oldest of 4 siblings: 3 girls, 1 boy. Younger sister of [52]. Social class V - father - occasional labourer. Normal pregnancy and labour. BW 2863 gm at 38 weeks' gestation. No motor or speech delay. No incoordination.

Medical known risk factors - none
other factors - none
Familial retardation - *both parents semi-literate*
- *1 sister [52] ESN/M.*

Case 52**Female****IQ 72**

Seen aged 9 years.

Mother and father aged 18 years, at birth. Oldest of 4 siblings; 3 girls, 1 boy. Older sister of [51]. Social class V - father - occasional labourer. Normal pregnancy; premature labour at 34 weeks' gestation, blue and limp at birth. No motor or speech delay. No incoordination.

Medical known risk factors - blue and limp at birth
other factors - none
Familial retardation - *both parents semi-literate*
- *1 sister [51] ESN/M.*

Case 53**Male****IQ 66**

Seen aged 7 years.

Mother aged 27 years, father aged 30 years, at birth. Elder of 2 male siblings. Social class III - father - civil servant. Normal pregnancy and labour. BW 2670 gm at 41 weeks' gestation. ? craniotabes at birth, but normal biochemistry and wrist x-ray. In special care for 1 week. No motor or speech delay. Poor coordination. Behaviour - inconsistent, erratic : obsession with numbers.

Medical

known risk factors

- none

other factors

- behavioural disturbance [DSM 312.10]

- incoordination

- small stature

Familial retardation

- none

Poor home circumstances

- lack of maternal 'bonding' and rapport.

Case No 54**Female****IQ 81**

Seen aged 10 years.

Mother aged 31 years, father aged 32 years, at birth. Second of 3 siblings: 2 girls, 1 boy. Social class II - father - company secretary. Normal pregnancy and labour - home delivery. BW 2891 gm at 41 weeks' gestation. No motor or speech delay. Mild incoordination.

Medical

known risk factors

- none

other factors

- incoordination

Familial retardation

- none : both parents achieved 'A' levels.

Case 55**Female****IQ 74**

Seen aged 7 years.

Mother aged 36 years, father aged 39 years, at birth. Youngest of 5 siblings: 3 girls, 2 boys. Social class IV - father - van driver. Normal pregnancy and labour. BW 2260 gm (<3rd centile) at 40 weeks' gestation. No motor or speech delay. Febrile fit at 8 months. No incoordination.

Medical

known risk factors

- none

other factors

- small-for-dates

- febrile fit

Familial retardation

- both parents semi-literate

- two brothers ESN/M.

Case 56**Male****IQ not tested**

Seen aged 6 years.

Mother and father aged 22 years, at birth. Second of 3 brothers - brother of [57]. Social class IV - father - van driver. Normal pregnancy. High forceps for fetal distress; BW 3610 gm on delivery at 38 weeks. Incubator for 3 days, on

oxygen. No motor or speech delay. In hospital for 2 weeks aged 22 months, with laryngeal stridor - in oxygen tent. Has severe asthma. No incoordination.

Medical known risk factors - fetal distress
other factors - [asthmatic]
Familial retardation - both parents semi-literate
- 1 brother [57] ESN/M.

Case 57**Male****IQ 66**

Seen aged 9 years.

Mother and father aged 19 years, at birth. Oldest of 3 male siblings - brother of [56]. Social class IV - father - van driver. Normal pregnancy: delivered by Caesarean section for brow presentation at 40 weeks' gestation. BW 3350 gm. No motor or speech delay. No incoordination.

Medical known risk factors - none
other factors - none
Familial retardation - both parents semi-literate
- 1 brother [56] ESN/M.

Case 58**Female****IQ 78**

Seen aged 9 years.

Mother aged 28 years, father aged 30 years, at birth. Three older maternal half-siblings; no full siblings. Social class V - father - occasional labourer. Mother anaemic in pregnancy. Normal delivery at 40 weeks' gestation. BW 2438 gm (<3rd centile). Early hypotonia, but no undue delay in motor or speech development. Insatiable appetite, behaviour at times disruptive. Obese - (weight

>97th centile, height and OFC on 50th centile): facial features of Prader-Willi syndrome, small hands and feet. Chromosomes 46 XX. No incoordination.

Medical known risk factors - Prader-Willi syndrome
other factors - anaemia in pregnancy
- small-for-dates
Familial retardation - father illiterate
- 1 half-sister ESN/M.

Case 59**Male****IQ 48**

Seen aged 9 years.

Mother aged 23 years, father aged 49 years, at birth. One older sister. Social class III - father - army corporal. Normal pregnancy and labour. BW 2870 gm at 37 weeks' gestation. Mild motor, moderate speech delay. Tongue tie released at 26 months. Behaviour thought to be disturbed from the age of 2 years - hyperkinetic. "Dizzy-spells" - ? petit mal epilepsy - from aged 6 years. EEG - showed minor

episodic changes. **Dysmorphic features** - long narrow face, telecanthus, long philtrum, very high arched palate. Bilateral clinodactyly. No asymmetry of chest wall but R.nipple higher than L. Poor coordination. **Chromosomes** - 46, XY, t(3;15)(p11;q21.2); familial translocation, found also in mother and maternal grandmother.

Medical	known risk factors	- none
	other factors	- familial translocation
		- petit mal
		- >3 dysmorphic features
Familial retardation		- none
Poor home circumstances		- mother depressed, repeated suicidal attempts.

Case 60**Male****IQ 63**

Seen aged 8 years.

Mother aged 22 years, father aged 26 years, at birth. One older sister - [119]. Social class IV - father - barman. Normal pregnancy. Spontaneous breech delivery at 36 weeks' gestation. BW 2863 gm. Treated neonatal jaundice. No motor, but some speech delay. Mild incoordination.

Medical	known risk factors	- none
	other factors	- neonatal jaundice
		- prematurity
		- incoordination
Familial retardation		- mother semi-literate
		- sister [119] - ESN/M.

Case 61**Female****IQ 70**

Seen aged 10 years.

Mother aged 34 years, father aged 36 years, at birth. Youngest of 3 siblings: 2 girls, 1 boy. Social class IV - father - lorry driver. Mother diabetic, on insulin, diagnosed aged 31 years, grossly obese, with erratic control. Normal pregnancy and labour. BW 3575 gm (>75th centile) at 40 weeks' gestation. No motor or speech delay. Two febrile fits aged 2 years: nine spontaneous grand mal fits over the next year. On phenobarbitone for 2 years: no fits since. No incoordination. Grossly obese - height on 10th centile, weight >97th centile.

Medical	known risk factors	- none
	other factors	- diabetic mother
		- epilepsy
Familial retardation		- mother semi-literate.

Case 62**Male****IQ 74**

Seen aged 9 years.

Mother aged 15 years, at birth, father's age unknown. Cared for by maternal grandmother, mother not seen: 2 half-siblings; one adopted, one in care - no details known. Social class V - grandfather - occasional labourer. Normal pregnancy and labour. BW 3400 gm at 40 weeks' gestation. No motor delay. Some speech delay. Mild incoordination.

Medical	known risk factors	- none
	other factors	- incoordination
Familial retardation		- mother and father both known to be ESN/M.

Case 63**Male****IQ 58**

Seen aged 9 years.

Mother aged 36 years, father aged 41 years, at birth. Elder of 2 male siblings. Social class III - father - planning estimator in NHS. Normal pregnancy. Spontaneous delivery at 36 weeks' gestation. BW 2850 gm (90th centile) : length 50 cm (90th centile) OFC - 34 cm (>90th centile). Motor and speech delay - walked unaided at 4 years, words only aged 3 years. Hospital investigation for delay Sotos syndrome diagnosed. Macrocephaly; long, narrow face; hypertelorism; long, pointed jaw; high arched palate; large hands and feet, poor speech. Gross incoordination.

Medical

known risk factors

- Sotos syndrome

other factors

- prematurity

Familial retardation

- mother ESN/M; features of Sotos syndrome

- brother at normal school, receiving special help.

Case 64**Male****IQ 71**

Seen aged 9 years.

Mother aged 23 years, father aged 30 years, at birth. Oldest of 3 siblings: 1 boy, 2 girls. Social class IV - father - factory worker. Normal pregnancy and labour. BW 3720 gm at 41 weeks' gestation. Mild motor and speech delay. Height on 3rd centile. No incoordination.

Medical

known risk factors

- none

other factors

- small stature

Familial retardation

- none.

Case 65**Male****IQ 69**

Seen aged 10 years.

Mother aged 32 years, father aged 31 years, at birth. Younger of 2 male siblings. Social class III - father - cable-joiner. Severe hyperemesis - no medication. Normal delivery at 39 weeks. BW 3240 gm. No motor delay : mild speech delay. No incoordination.

Medical

known risk factors

- none

other factors

- hyperemesis

Familial retardation

- none.

Case 66**Female****IQ 56**

Seen aged 9 years.

Mother aged 27 years, father aged 28 years, at birth. Second of 3 female siblings. Social class III - father - car-mechanic. Mother in car accident with blow to abdomen, at 16 weeks' gestation: no bleeding. Normal delivery at 40 weeks' gestation. BW 2778 gm (>10th centile). No motor or speech delay. No incoordination.

- 3 dysmorphic features
- incoordination
- epilepsy
- behavioural disturbance [DSM 312.10]
- *none.*

Familial retardation**Case 70****Female****IQ 52**

Seen aged 11 years.

Mother aged 29 years, father aged 30 years, at birth. Third of 5 siblings: 3 boys, 2 girls. Social class III - father - stevedore. Normal pregnancy and labour. BW 3400 gm at 42 weeks' gestation. No motor or speech delay. No incoordination.

Medical known risk factors - none
 other factors - none

Familial retardation - *both parents ESN/M*
 - *two brothers ESN/M.*

Case 71**Male****IQ 75**

Seen aged 11 years.

Mother aged 36 years, father aged 37 years, at birth. Youngest of 7 siblings: 5 boys, 2 girls. Social class V - father - farm worker. Threatened labour at 6 months gestation with some bleeding, bleeding again at 8 months. Induced at 38 weeks' - normal delivery. BW 2750 gm : in special care for 3 days. No motor or speech delay. Reaction at 1 year to 2nd immunisation, with fitting. Height on 3rd centile. No incoordination.

Medical known risk factors - none
 other factors - bleeding in pregnancy
 - immunisation reaction
 - short stature

Familial retardation - *father ESN/M*
 - *brother ESN/M.*

Case 72**Male****IQ 69**

Seen aged 11 years.

Mother aged 25 years, father aged 28 years, at birth. Second of 3 male siblings; also 2 younger maternal half-siblings; 1 boy, 1 girl. Social class IV - step-father - unemployed butcher. Normal pregnancy and labour. BW. 4564 gm (90th centile) at 40 weeks' gestation. No motor delay. Slow to speak - received pre-school speech therapy. No incoordination.

Medical known risk factors - none
 other factors - none

Familial retardation - *mother semi-literate*
Poor home circumstances - *apathetic, inadequate mother.*

Case 73**Female****IQ 67**

Seen aged 9 years.

Mother aged 19 years, at birth, father's age unknown. One younger female maternal half-sibling. Social class V - stepfather - labourer. Normal pregnancy and labour. BW 3760 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical

known risk factors - none

other factors - none

Familial retardation- *mother semi-literate.***Case 74****Female****IQ 58**

Seen aged 11 years.

Mother aged 28 years, father aged 27 years, at birth. Youngest of 3 siblings: 2 boys, 1 girl. Social class III - father - HGV driver. Mother bitten by a dog in the 4th month of pregnancy. Rapid delivery at 42 weeks: BW 2610 gm (<10th centile). Toxoplasmosis diagnosed when 9 months old following referral for nystagmus and large anterior fontanelle. Titre >1:2000. Severe scarring of both maculae, intracranial calcification. Global retardation. Grand mal epilepsy from 4-9 years. Precocious puberty at 7 years. Registered blind - very limited peripheral vision only. Mild ataxia, with poor coordination. Difficult, unpredictable behaviour.

Medicalknown risk factors - toxoplasmosis

other factors - incoordination

- epilepsy

- behaviour disorder [DSM 312.10]

Familial retardation- *none.***Case 75****Male****IQ 69**

Seen aged 9 years.

Mother aged 21 years, father aged 24 years, at birth. No full siblings: 2 paternal half-siblings, 1 boy, 1 girl. Cared for by father and stepmother, but mother also seen. Social class V - father - labourer. Severe hyperemesis throughout pregnancy - no medication. High forceps delivery - fetal distress recorded. BW 4640 gm (97th centile) at 42 weeks' gestation. No motor or speech delay. No incoordination.

Medicalknown risk factors - fetal distress

other factors - hyperemesis

Familial retardation- *none.***Case 76****Male****IQ 68**

Seen aged 9 years.

Mother aged 19 years, father aged 26 years, at birth. Second of 3 male siblings. Social class III - father - roofing felter. Normal pregnancy and labour. BW 3200 gm at 40 weeks' gestation. No motor, but some speech delay. Bilateral

orchidopexy and herniotomies aged 6 and 7 years. Aarskog syndrome diagnosed when seen - hypertelorism - bilateral ptosis; shallow orbits; epicanthic folds; short, stubby fingers and toes; minimal interdigital webbing; small scrotum. Bilateral ptosis and hypertelorism in 1 brother. Unilateral ptosis (treated operatively) in mother and maternal grandmother. No incoordination.

Medical known risk factors - Aarskog syndrome
other factors - none

Familial retardation - none

Case 77**Male****IQ 74**

Seen aged 9 years.

Mother and father both aged 27 years, at birth. Second of 4 siblings: 1 older brother, younger twin sisters. Social class IV - father - welder. Normal pregnancy and labour. BW 4000 gm at 40 weeks' gestation. No motor delay - some speech delay with minor degree of tongue tie. No incoordination.

Medical known risk factors - none
other factors - none

Familial retardation - none

Case 78**Female****IQ 57**

Seen aged 10 years.

Mother aged 20 years, father aged 31 years, at birth. One younger brother. Social class III - father - glass-worker. Toxaemia in pregnancy. Fetal distress - forceps delivery following 2nd stage delay. BW 3260 gm at 40 weeks' gestation. No motor, some speech delay. No incoordination.

Medical known risk factors - fetal distress
other factors - toxaemia

Familial retardation - *mother semi literate.*

Case 79**Female****IQ 70**

Seen aged 11 years.

Mother aged 29 years, father aged 31 years, at birth. Youngest of 3 siblings: 2 girls, 1 boy. Social class IV - father - taxi driver. Recurrent bleeding in pregnancy, with 6 hospital admissions. Ruptured membranes at 30 weeks. Normal delivery at 42 weeks. BW 3865 gm. Meningitis diagnosed when 8 weeks old - macular rash, vomiting, cerebral imitation. No growth obtained from CSF or blood cultures. No motor or speech delay. No incoordination.

Medical known risk factors - meningitis
other factors - threatened abortion.

Familial retardation - none.

Case 80**Female****IQ 68**

Seen aged 9 years.

Mother aged 24 years, father aged 30 years, at birth. Two older brothers. Social class IV - father - labourer. Normal pregnancy and labour. BW 2720 gm (<10th centile) at 40 weeks' gestation. Paediatric investigation at 11 months for delayed development - OFC on 3rd centile, skull and chest x-ray normal, rubella and CMV titres normal. At 17 months, was at 7-9 months stage of development, OFC still on 3rd centile, thyroid functions and chromosomes normal. Two Grand mal fits aged 6 years - normal EEG. On sodium valproate for 2 years - no further fits. OFC on 3rd centile when seen but in keeping with height (10th centile) and weight (10th centile). Asymmetric skull and mild hypertelorism. Hyperactive behaviour. No incoordination.

Medical known risk factors - none
 other factors - low birth weight
 - idiopathic epilepsy
 - behaviour disorder [DSM 312.10]
 - skull asymmetry
Familial retardation - none.

Case 81**Male****IQ 74**

Seen aged 8 years.

Mother aged 20 years, father aged 26 years, at birth. Two older paternal half-sisters, 2 full sisters - one older, one younger, and 1 male twin - [82] - non-identical. Social class V - father - unemployed labourer. Twin pregnancy - normal delivery (1st twin) at 33 weeks' gestation. BW 2330 gm (50th centile). In SCBU for 2 months - no problems. Admitted aged 8 months with gross wasting - weight 5030 gm and suspected non-accidental injury. Discharged aged 10 months - weight 7780 gm. Skeletal survey normal. No motor delay. Speech delayed - still indistinct when seen. Height and weight <3rd centile. OFC on 3rd centile when seen. No incoordination.

Medical known risk factors - none
 other factors - twin pregnancy
 - premature birth
 - gross malnutrition in infancy
Familial retardation - both parents illiterate
 - 4 of 5 siblings ESN/H
Poor home circumstances - domineering father,
 - inadequate deaf mother.

Case 82**Male****IQ 58**

Seen aged 8 years.

Mother aged 20 years, father aged 26 years, at birth. Two older paternal half-sisters, 2 full sisters, 1 younger, 1 older and 1 male twin - [81] - non-identical. Social class V - father - unemployed labourer. Twin pregnancy. Emergency caesarean section for prolapsed cord at 33 weeks' gestation (2nd twin) and Apgar score 6 at 5 minutes. BW 1680 gm (10th centile). In SCBU for 2 months - no problems. Admitted aged 8 months with severe malnutrition - weight 3940 gm and suspected non-accidental injury. Discharged aged 10 months - weight 6900 gm. Skeletal survey normal. No motor delay. Speech delayed, still indistinct when seen. At examination, height and

weight <3rd centile, OFC on 3rd centile. No incoordination.

- Medical**
- | | |
|--------------------|---------------------------------|
| known risk factors | - low Apgar score |
| other factors | - twin pregnancy |
| | - premature birth |
| | - gross malnutrition in infancy |
- Familial retardation**
- both parents illiterate
 - 4 of 5 siblings ESN/M
- Poor home circumstances**
- domineering father,
 - inadequate, deaf mother.

Case 83**Male****IQ 80**

Seen aged 11 years.

Mother aged 29 years, father aged 56 years, at birth. Father died 6 months later. Mother epileptic since childhood, on phenytoin and phenobarbitone. Youngest of 4 siblings: 3 boys, 1 girl. Social class IV - father - stevedore. Normal pregnancy (anti-epileptic medication). Elective Caesarean delivery at 37 weeks. BW 2834 gm. No motor or speech delay. No incoordination.

- Medical**
- | | |
|--------------------|----------------------------------|
| known risk factors | - none |
| other factors | - epileptic mother on medication |
- Familial retardation**
- mother semi-literate
 - 1 sister ESN/M.

Case 84**Male****IQ 76**

Seen aged 11 years.

Mother aged 25 years, father aged 37 years, at birth. Third of 4 male siblings. Social class IV - father - milkman. Ante-partum haemorrhage 3 days before birth - low forceps delivery, at 40 weeks' gestation. BW 3310 gm. Floppy baby - mild, early motor delay, but walked at 14 months. No speech problems. No incoordination.

- Medical**
- | | |
|--------------------|---------------------------|
| known risk factors | - none |
| other factors | - ante-partum haemorrhage |
- Familial retardation**
- none.

Case 85**Male****IQ 72**

Seen aged 10 years.

Mother aged 20 years, father aged 31 years, at birth. Second of 4 siblings: 2 girls, 2 boys. Social class IV - father - stevedore. Normal pregnancy and labour. BW 3175 gm at 40 weeks' gestation. No motor or speech delay. Non-accidental injury at 14-15 months. No incoordination. Small stature - height well below 3rd centile.

- Medical**
- | | |
|--------------------|-----------------|
| known risk factors | - none |
| other factors | - small stature |
- Familial retardation**
- father illiterate
- Poor home circumstances**
- father schizophrenic, unpredictable
 - mother unsupportive.

Case 86**Female****IQ 59**

Seen aged 9 years.

Mother aged 18 years, father aged 24 years, at birth. Second of 3 female siblings. Social class V - father - labourer. Normal pregnancy. Rapid home birth at 38 weeks - BW 2579 gm. In SCBU for 2 days, but no neonatal problems noted. Admitted aged 4 months, for failure to thrive - mother unable to cope. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- precipitate delivery
Familial retardation		- <i>mother illiterate</i>
Poor home circumstances		- domineering, abusive father
		- inadequate mother.

Case 87**Female****IQ 64**

Seen aged 12 years.

Mother aged 28 years, father aged 30 years, at birth. Youngest of 5 siblings - 4 older brothers. Social class V - father - labourer. Normal pregnancy and labour. BW 4110 gm (97th centile) at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- <i>mother ESN/M</i>
		- <i>father semi-literate</i>
		- <i>three of four brothers ESN/M.</i>

Case 88**Male****IQ 59**

Seen aged 8 years.

Mother aged 26 years, father aged 23 years, at birth. Second of 3 male siblings, 1 brother [89]. Social class V - father - labourer. Normal pregnancy. Forceps breech delivery at 40 weeks' gestation. BW 3720 gm. No motor or speech delay. Macrocephaly - OFC >97th centile, at 55 cm. Thin upper lip, low hair growth on brow. No incoordination.

Medical	known risk factors	- none
	other factors	- macrocephaly
Familial retardation		- <i>both parents semi-literate</i>
		- <i>1 brother [89] ESN/M.</i>

Case 89**Male****IQ 53**

Seen aged 10 years.

Mother aged 24 years, father aged 21 years, at birth. Eldest of 3 male siblings - 1 brother [88]. Social class V - father - labourer. Low forceps delivery at 34 weeks' gestation. BW 2012 gm. No motor or speech delay. Macrocephaly - OFC 57.4 cm, well above 97th centile. Low hair growth on forehead, thin upper lip (similar to younger brother). No incoordination.

Case 93**Male****IQ 75**

Seen aged 9 years.

Mother aged 26 years, father aged 32 years, at birth. Youngest of 5 siblings: 3 boys, 2 girls. Social class V - father - labourer. Normal pregnancy and labour. BW 3320 gm at 42 weeks' gestation. No motor or speech delay, but speech slow, hesitant when seen. No incoordination.

Medical

known risk factors - none
other factors - none

Familial retardation- *both parents semi-literate.***Case 94****Male****IQ 61**

Seen aged 9 years.

Mother aged 41 years, father aged 29 years, at birth. One half-brother, 20 years older; 7 spontaneous abortions between the 2 births. Social class IV - father - golf course attendant. Normal pregnancy. Assisted breech delivery at 40 weeks' gestation. Apgar score 6 at 5 minutes. BW 2070 gm (<3rd centile). In SCBU for 8 days - because of low birth weight. No motor, but some speech delay. Height and OFC when seen, on 3rd centile.

Medical

known risk factors - low Apgar score
other factors - low birth weight
- small stature

Familial retardation- *mother semi-literate.***Case 95****Male****IQ 75**

Seen aged 10 years.

Mother aged 22 years, father aged 26 years, at birth. One younger sister. Social class IV - father - fibre-glass laminater. Normal pregnancy and labour. BW 4000 gm at 40 weeks' gestation. No motor or speech delay, but poor articulation when seen. No incoordination.

Medical

known risk factors - none
other factors - none

Familial retardation- *father illiterate***Poor home circumstances**

- history of non-accidental injury with little maternal rapport.

Case 96**Male****IQ 69**

Seen aged 10 years.

Mother aged 26 years, father aged 29 years, at birth. Mother diabetic since childhood - stable control with insulin. Fourth of 5 siblings: 3 girls, 2 boys. Social class IV - father - labourer. Diabetic control satisfactory in pregnancy.

Normal delivery at 40 weeks' gestation. BW 4770 gm (>97th centile). No motor, but speech delay. Asymmetric chest - R. shoulder narrower and higher than the L. R. nipple higher than L., and mild scoliosis.

Medical known risk factors - none
other factors - maternal diabetes

Familial retardation - *father illiterate,*
- *mother semi-literate*
- *1 brother ESN/M.*

Case 97**Female****IQ 65**

Seen aged 7 years.

Mother aged 20 years, father aged 29 years, at birth. One younger brother and sister. Social class V - father - storeman. Oral contraceptive pill taken for first 3 months of pregnancy. Low forceps delivery at 40 weeks' gestation. BW 3430 gm. Apgar score 6 at 5 minutes. No motor or speech delay. Screaming fits investigated at age 5 years. Amino acids, mucopolysaccharides, EEG, bone age - all normal. Coordination unimpaired.

Medical known risk factors - low Apgar score
other factors - hormone medication in pregnancy

Familial retardation - *none.*

Case 98**Female****IQ 70**

Seen aged 10 years.

Mother aged 27 years, father aged 33 years, at birth. Two older brothers, 1 younger sister. Mother - known alcoholic - not seen. Children in care of father. Social class V - father - casual labourer. Heavy alcohol intake in pregnancy. Ante partum haemorrhage at 39 weeks - delivered by Caesarean section through placenta praevia. BW 1930 gm (<3rd centile). Paediatric check at 10 weeks - satisfactory. No motor or speech delay. Features of fetal alcohol syndrome - high hairline, small palpebral fissures, long philtrum, maxillary hypoplasia. Height and OFC both on 3rd centile. No incoordination.

Medical known risk factors - fetal alcohol syndrome
other factors - ante-partum haemorrhage

Familial retardation - *both parents semi-literate*

Poor home circumstances - inadequate, apathetic father.

Case 99**Female****IQ 63**

Seen aged 10 years.

Mother aged 31 years, father aged 38 years, at birth. One older brother and sister. Social class IV - father - taxi-driver. Bleeding at 28 weeks' gestation. Normal delivery at 39 weeks' gestation. BW 2608 gm (<10th centile). No motor delay, but some speech delay. Seen by paediatrician at 2 years of age for failure to thrive - nil found. One febrile fit at age 2 years. Height and weight below

3rd centile, OFC on 3rd centile. Bird-like face, prominent nasal bridge, relatively large nose, thin lips. Asymmetric chest wall - R. shoulder and nipple higher than L., and L. chest wall flatter. No scoliosis. Bilateral clinodactyly. No incoordination.

Medical known risk factors - none
 other factors - ante-partum haemorrhage
 - >3 dysmorphic features
 - small stature
 - febrile fit

Familial retardation - none.

Case 100**Female****IQ 69**

Seen aged 11 years.

Mother aged 33 years, father aged 34 years, at birth. Youngest of 4 siblings: 2 boys, 2 girls. Social class IV - father - fitter's mate. Normal pregnancy. Ante-partum haemorrhage 5 hours before normal delivery at 40 weeks' gestation. BW 2900 gm. No motor, mild speech delay. No incoordination.

Medical known risk factors - none
 other factors - ante-partum haemorrhage

Familial retardation - none.

Case 101**Male****IQ 73**

Seen aged 11 years.

Mother aged 24 years, father aged 27 years, at birth. One older brother, two younger maternal half-brothers. Social class III - father - printer. Cared for in local authority home, occasional home visits at weekends. Mother seen at home. Normal pregnancy. Premature labour at 34 weeks' gestation. Cord round neck: Apgar score 5 at 5 minutes. Apnoeic for 3 minutes. BW 2070 gm. In SCBU for 5 weeks - developed respiratory distress syndrome. Readmitted aged 7 weeks with

R. lobar pneumonia - discharged aged 10 weeks. Seen by paediatrician at 11 months, because of failure to thrive. Grand mal fits at 22 and 23 months - on phenytoin till aged 4 years. EEG showed no focal abnormality. Hyperactive, difficult behaviour, self-inflicted skin lesions. Severe myopia. Poor coordination of eye movements when seen, mild chest wall asymmetry. R. Simian crease. Poor coordination.

Medical known risk factors - low Apgar score
 other factors - premature birth
 - early chest infections
 - epilepsy
 - behaviour disorder [DSM - 307.30, 312.10, 314.01]
 - incoordination

Familial retardation - none.

Case 102**Male****IQ 56**

Seen aged 8 years.

Mother aged 19 years, father aged 22 years, at birth. One younger sister and brother. Social class IV - father - railway worker. Normal pregnancy. Premature delivery at 36 weeks' gestation. BW 1780 gm (<3rd centile). Right cleft palate and hare lip. In SCBU for 5 weeks. Palate and lip repaired at 6 months and 1 year old. No motor delay, but some speech delay - indistinct when seen. No incoordination.

Medical

known risk factors

- none

other factors

- premature delivery

- low birth weight

- cleft lip and palate

Familial retardation

- none.

Case 103**Male****IQ 69**

Seen aged 7 years.

Mother aged 22 years, father aged 29 years, at birth. Social class V - father - dustman. Normal pregnancy. Premature delivery at 34 weeks' gestation, low forceps. BW 2250 gm. In SCBU for 2 weeks. No motor, but some speech delay - articulation poor, height on 3rd centile, weight and OFC on 10th, when seen. Poor coordination.

Medical

known risk factors

- none

other factors

- premature delivery

- small stature

- incoordination

Familial retardation

- none.

Case 104**Female****IQ 75**

Seen aged 11 years.

Mother and father both aged 33 years, at birth. Three older sisters. Social class IV - father - school janitor. Toxaemia in pregnancy. Rapid hospital delivery at 40 weeks' gestation. BW 4210 gm. Some neonatal hypotonia. No motor delay. Some speech delay. Cohen syndrome diagnosed when seen - heavily built girl with prominent incisor teeth, pigmentation on periphery of R.retinal disc, R.Simian crease, mild hypotonia and hyperextensible joints. No incoordination.

Medical

known risk factors

- Cohen syndrome

other factors

- toxaemia

Familial retardation

- none.

Case 105**Male****IQ 57**

Seen aged 11 years.

Mother aged 23 years, father aged 39 years, at birth. Two younger sisters. Social class IV - father - assembly worker. Normal pregnancy and labour. BW 3200

gm at 40 weeks' gestation. No motor delay. Speech poor - seen by paediatrician at age 3 years; thyroid function and amino acids normal. Admitted to pre-school assessment unit - ?autistic, but improved. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- <i>father semi-literate</i>

Case 106

Male

10 72

Seen aged 7 years.

Mother aged 24 years, father aged 20 years, at birth. Two younger brothers. Social class IV - father - stevedore. Normal pregnancy and labour. BW 3800 gm at 41 weeks' gestation. No motor, some speech delay. No incoordination. **Chromosome analysis - 47.XXY.**

Medical known risk factors - 47,XXY - Klinefelter's syndrome
other factors - none

Familial retardation - mother semi-literate.

Case 107

Female

10 66

Seen aged 11 years.

Mother aged 39 years, father aged 38 years, at birth. Youngest of 6 siblings: 5 girls, 1 boy. Social class IV - father - stevedore. Toxaemia in pregnancy - in hospital 1 month prior to delivery at 42 weeks' gestation. Spontaneous breech delivery - birth anoxia. Apgar score 4 at 5 minutes. BW 2780 gm (<10th centile). Nursed in incubator for 1 week. No motor or speech delay. No incoordination. Heavily built girl - height and OFC on 50th centile, weight on 97th centile.

Chromosomes - 46,XX,del 15q 12, in all cells examined. This deletion is found in Prader-Willi syndrome, but although obese, this girl did not have the facial features or excessive appetite associated with that syndrome. Two of 225 cells analysed in the original blood sample showed the *fragile-X* chromosome. No *fragile-X* chromosomes were found in 100 cells analysed in a repeat specimen, and the finding of 2 positive cells was not regarded as significant. **Parents:** - mother 46,XX : father 46,XY.

Medical	known risk factors	- <u>chromosome deletion</u>
		- <u>low Apgar score</u>
	other factors	- toxæmia
Familial	retardation	- none

Case 108

Female

10 58

Seen aged 10 years.

Mother aged 32 years, father aged 30 years, at birth. One older brother and sister. Social class IV - father - Remploy machinist. Normal pregnancy and labour. BW 2820 gm at 40 weeks' gestation. No motor, but mild speech delay. Height and weight below 3rd centile. OFC on 50th centile. No incoordination.

Medical	known risk factors	- none
	other factors	- small stature
Familial retardation		- mother ESN/M
Poor home circumstances		- depressed mother, with history of suicide attempts.

Case 109**Male****IQ 70**

Seen aged 8 years.

Mother aged 25 years, at birth, father's age not known. No siblings. Social class III - stepfather - electrician. Toxaemia in pregnancy - labour induced at 37 weeks' gestation. Caesarean section for failure to progress. BW 3110 gm (75th centile). Apgar score 6 at 5 minutes. No motor, but some speech delay. Large, obese child - height - 75th centile : weight >97th centile, OFC - 90th centile.

Face and body appearance suggestive of Prader-Willi syndrome, but birth weight on 75th centile, no history of early hypotonia, of excessive appetite or behavioural disturbance - hence insufficient grounds for a firm diagnosis. No incoordination.

Medical	known risk factors	- low Apgar score
	other factors	- toxaemia
Familial retardation		- none.

Case 110**Male****IQ 75**

Seen aged 9 years.

Mother aged 26 years, father aged 27 years, at birth. Third of 4 siblings: 3 boys, 1 girl. Social class III - father - control inspector in car factory. Normal pregnancy and labour. BW 3500 at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- mother semi-literate
		- 1 brother ESN/M.

Case 111**Female****IQ 74**

Seen aged 11 years.

Mother aged 48 years, father aged 52 years, at birth, died 2 years later. Youngest - by 14 years - of 4 siblings: 3 boys, 1 girl. Social class IV - stepfather - bus driver. Hyperemesis and mild hypertension in pregnancy. Induced at 40 weeks' gestation - normal delivery. BW 3040 gm. Down syndrome diagnosed neonatally - 47,XX,+21. No undue motor, but speech delay. Facial appearance characteristic of Down syndrome; flat occiput, clinodactyly, gap between 1st and

2nd toes. No Brushfield's spots or Simian creases. Height on 50th centile, weight and OFC on 75th. Poor coordination.

Medical	known risk factors	- Down syndrome
	other factors	- hyperemesis
		- incoordination
Familial retardation		- none.

Case 112**Female****IQ 54**

Seen aged 12 years.

Mother aged 26 years, father aged 27 years, at birth. Fourth of 6 siblings: 5 boys, 1 girl; sister of [113] and [114]. Social class V - father - unemployed labourer, not living with the family. Normal pregnancy and labour. BW 2680 gm at 38 weeks' gestation. Mild motor and speech delay. Height below 3rd centile, weight on 10th centile, OFC on 50th centile. No incoordination.

Medical known risk factors

- none

other factors

- small stature

Familial retardation

- both parents illiterate

- 4 brothers ESN/M, [113], [114].

Very poor home circumstances

- inadequate, depressed mother, barely able to cope on her own.

Case 113**Male****IQ 63**

Seen aged 10 years.

Mother aged 28 years, father aged 29 years, at birth. Identical twin of [114], brother of [112]. Four older siblings: 3 boys, 1 girl. Social class V - father - unemployed labourer, separated from mother. Twin pregnancy. Breech extraction (2nd twin) at 36 weeks' gestation. BW 2520 gm. Treated neonatal jaundice, discharged home when 8 days old. Readmitted aged 3 weeks, with chest infection and failure to thrive. Further hospital admission aged 18 months old for failure

to thrive - no weight gain since 11 months old, and frequent diarrhoea. Fall at home aged 15 months - unconscious for 24 hours, followed by 2 grand mal fits: none since. Some motor and speech delay. Height and weight well below 3rd centile, OFC just >50th centile. No incoordination.

Medical known risk factors

- none

other factors

- twin pregnancy

- malnutrition in infancy

- head injury aged 15 months with 2 grand mal fits

- small stature

Familial retardation

- both parents illiterate

- 3 brothers, 1 sister ESN/M, [112] + [114].

Very poor home circumstances

- inadequate, depressed mother, barely able to cope on her own.

Case 114**Male****IQ 58**

Seen aged 10 years.

Mother aged 28 years, father aged 29 years, at birth. Identical twin of [113], brother of [112]. Four older siblings: 4 boys, 1 girl. Social class V - father - unemployed labourer, separated from mother. Twin pregnancy. Normal delivery (1st twin) at 36 weeks' gestation. Treated neonatal jaundice. Discharged home when 8 days old. Readmitted aged 3 weeks with chest infection and failure to thrive, and again, with twin brother, at 18 months. One febrile convulsion at 16 months - associated with otitis media. Some motor and speech delay. Height and weight well below 3rd centile, OFC on 50th centile. No incoordination.

- Medical** known risk factors - none
 other factors - twin pregnancy
 - malnutrition in infancy
 - febrile fit
 - small stature
- Familial retardation** - both parents illiterate
 - 3 brothers, 1 sister ESN/M, [112], [113].
- Very poor home circumstances** - inadequate, depressed mother, barely able to cope on her own.

Case 115**Female****IQ 64**

Seen aged 9 years.

Mother aged 35 years, father aged 37 years, at birth. Parents double first cousins - fathers were brothers, and mothers were sisters. Third of 5 siblings: 3 boys, 2 girls. Social class IV - father - spare parts man in factory. Normal pregnancy and labour. BW 3470 gm at 41 weeks' gestation. Clitoral hypertrophy and labial fusion noted at birth. Chromosomes - 46 XX. Neonatal twitching; vomiting started on day 5, severe by day 7, with loss of weight. Congenital adrenal hyperplasia diagnosed, but biochemical control difficult to establish. In SCBU for 6 weeks. Also found to have congenital abnormality of 4th rib, L.congenital glaucoma - successful geniotomy. Readmitted aged 7 weeks, with opisthionos, fitting followed steroid reduction, and L.facial palsy, with convergent squint. Adequate control still difficult to establish; she remained irritable, with poor head control and increased tone. When seen at 7 months old, there was failure of growth, with a bone age of 3 months: the left facial palsy was still present, and she was Cushingoid and hirsute. Control of salt-losing state has been erratic since, with delay in motor and speech development. When seen, appeared Cushingoid and hirsute; partial L.facial palsy, L.internal strabismus. Height - 25th centile, weight - >90th centile, OFC - 90th centile. She had a low hair line, very short neck, R.single palmar crease. Coordination was grossly impaired.

- Medical** known risk factors - neurological sequelae of congenital adrenal hyperplasia
 - neonatal twitching : crisis at 7 weeks
 other factors - incoordination.
- Familial retardation** - none.

Two younger siblings also have congenital adrenal hyperplasia, but have been well controlled with medication.

Case 116**Female****IQ 80**

Seen aged 9 years.

Mother aged 18 years, father aged 31 years, at birth. One younger brother. Social class V - father - dustman. Mother not living with the family - not seen. Normal pregnancy and labour. BW 2929 gm at 40 weeks' gestation. No motor, but some speech delay. No incoordination.

- Medical** known risk factors - none
 other factors - none
- Familial retardation** - father semi-literate.

Case 117**Male****IQ 71**

Seen aged 9 years.

Mother aged 26 years, father aged 28 years, at birth. One older sister and brother. Social class III - father - decorator. Normal pregnancy and labour. BW 3620 gm at 39 weeks' gestation. Early development up to dates. Found cold and limp in pram, not breathing, when aged 6 months; resuscitated by father, took about 5 minutes before breathing restarted. No hospital admission. Slight motor delay thereafter, more marked speech delay, especially articulation. Behaviour disturbance, with erratic, unpredictable behaviour and difficult to control both at home and at school. No incoordination.

Medical

known risk factors

- postnatal prolonged apnoea

other factors

- behaviour disturbance [DSM 312.10]

Familial retardation- *none.***Case 118****Female****IQ 61**

Seen aged 12 years.

Mother aged 26 years, father aged 30 years, at birth. Fourth of 5 female siblings. Social class V - father - labourer. No problems in pregnancy; normal delivery at 35 weeks' gestation, in Ireland. BW 2636 gm. Twitching with blue turns noted on day 3 - blood sugar normal. Readmitted aged 2 weeks with fitting after feeds - nil abnormal found. No fits since. No motor or speech delay. No incoordination.

Medical

known risk factors

- neonatal twitching

other factors

- *none***Familial retardation**- *father semi-literate*- *1 older sister ESN/M; she also had neonatal twitching.***Case 119****Female****IQ 73**

Seen aged 11 years.

Mother aged 18 years, father aged 22 years, at birth. One younger brother [60]. Social class IV - father - barman. Normal pregnancy. Fetal distress recorded - low forceps delivery. BW 3230 gm at 40 weeks' gestation. No motor or speech delay. Mild incoordination; with poor balance - heel-toe walking.

Medical

known risk factors

- fetal distress

other factors

- incoordination

Familial retardation- *mother semi-literate*- *brother [60] ESN/M.***Case 120****Female****IQ 63**

Seen aged 10 years.

Mother aged 21 years, father aged 22 years, at birth. One younger sister. Social class V - father - unemployed. Normal pregnancy, fetal distress recorded at birth, at 40 weeks' gestation, with meconium-stained liquor. Delivery by Kielland's forceps. Did not breathe for 4 minutes, although Apgar score of 8 recorded at 5

minutes. BW 2700 gm (<10th centile). OFC (<3rd centile). When seen at 8 months old, not yet sitting, height, weight, OFC all below 3rd centile. Walked at 20 months, speech delayed till 2 years old. Height when seen, well below 3rd centile, weight on 50th centile, OFC on 25th centile. No incoordination.

Medical known risk factors - fetal distress
other factors - small stature

Familial retardation - mother illiterate
- father semi-literate
- sister ESN/M.

Case 121**Female****IQ 67**

Seen aged 9 years.

Mother aged 21 years, father aged 28 years, at birth. One younger sister. Social class III - father - service engineer. Severe hyperemesis requiring several hospital admissions during pregnancy. Bleeding for 2 days at 15 weeks' gestation. Normal delivery at 38 weeks' gestation. BW 2920 gm. No motor or speech delay. No incoordination.

Medical known risk factors - none
other factors - hyperemesis
- threatened abortion

Familial retardation - mother semi-literate.

Case 122**Female****IQ 60**

Seen aged 7 years.

Both parents aged 28 years, at birth, in India. No known consanguinity. Third born of 6 female siblings. Social class V - father - labourer. Mother spoke poor English, could give no details of pregnancy or labour, but child known to be very small at birth. Seen, in England, at 4 years old, for gross global delay; small stature and OFC of 43.9 cm recorded. All investigations, including bone age, normal. Height, when seen, just below 10th centile, but weight below 3rd centile, and OFC markedly reduced at 47 cm. Little speech. Poor cooperation - coordination not tested.

Medical known risk factors - microcephaly
other factors - small stature

Familial retardation - none.

Case 123**Female****IQ 57**

Seen aged 12 years.

Mother aged 23 years, father aged 32 years, at birth. Older of 2 female siblings. Mother remarried, living elsewhere, not seen. Social class V - father - unemployed labourer. Normal pregnancy and labour. BW 3010 gm at 41 weeks' gestation (information from hospital case notes). Motor and speech delay - seen at 4 years old with global retardation - no medical reason found. Incoordinated with clumsy gait.

Medical known risk factors - none
other factors - incoordination

Familial retardation

- both parents ESN/M

- sister ESN/M.

Poor home circumstances

- cared for by depressed, apathetic, inadequate father.

Case 124**Male****IQ 59**

Seen aged 11 years.

Mother aged 26 years, father aged 27 years, at birth, in Australia. One younger sister. Social class II - father - industrial engineer. Toxaemia from 35 weeks' gestation. Placental insufficiency - induced at 37 weeks' gestation, forceps delivery for brow presentation. BW 2863 gm. Treated neonatal jaundice. Poor feeder, but no delay in early development. Febrile convulsion at 14 months (in Britain) developed into status epilepticus, which proved very difficult to control, and lasted 3-4 days in spite of hospital treatment. Frequent grand mal fits over next year. On anti-convulsant treatment till aged 4 years; no fits since. EEG - aged 5 years - showed no paroxysmal activity. Behaviour problems - irrational anger, lack of eye contact, elaborate fantasies, rapid flitting from subject to subject. Macrocephaly, with OFC of 59 cm. Marked incoordination - very poor at hopping and heel-toe walking.

Medical

known risk factors

- status epilepticus

other factors

- toxaemia

- jaundice

- behaviour problems [DSM 312.10]

- incoordination

Familial retardation

- none.

Case 125**Male****IQ 85**

Seen aged 7 years.

Mother aged 23 years, father aged 24 years, at birth. Twin sister, and younger sister and brother. Social class III - father - plant operator foreman. Twin pregnancy, chlomiphene induced following 6 years infertility. Spontaneous labour at 31 weeks' gestation, vertex delivery (1st twin). BW 1690 gm. Apnoeic spells during first few days. Home when 11 weeks old - satisfactory progress. Motor and speech development - mild delay, noted to be slower than twin. Occasional attacks of pallor and limpness; normal skull x-ray, EEG and brain scan - not thought to have epilepsy. No incoordination.

Medical

known risk factors

- neonatal apnoeic attacks

other factors

- twin pregnancy

- premature delivery

- low birth weight

Familial retardation

- none.

Case 126**Male****IQ 76**

Seen aged 7 years.

Mother aged 18 years, father aged 20 years, at birth. No siblings. Social class V - father - (divorced) labourer. Hyperemesis in pregnancy. Normal delivery at 41 weeks' gestation. BW 3730 gm. No motor, mild speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- hyperemesis
Familial retardation		- none.

Case 127**Male****IQ 68**

Seen aged 10 years.

Mother and father both aged 25 years, at birth. One younger brother. Social class III - father - radio producer. Normal pregnancy and labour. BW 3373 gm at 40 weeks' gestation. L.cleft lip and palate, repaired at 4 months. No motor, mild speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- cleft lip and palate
Familial retardation		- none.

Case 128**Female****IQ 75**

Seen aged 9 years.

Mother aged 18 years, father aged 28 years, at birth. One younger brother. Social class III - father - (divorced) HGV driver. Normal pregnancy and labour. BW 3200 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- none.

Case 129**Male****IQ 75**

Seen aged 11 years.

Mother aged 26 years, father aged 30 years, at birth. Second of 3 siblings: older sister, younger infant brother. Social class III - father - HGV driver. Normal pregnancy and labour. BW 2400 gm (<10th centile) at birth. No motor or speech delay. No incoordination. Bifid right thumb (repaired) and broad 1st toes - both also present in father and sister.

Medical	known risk factors	- none
	other factors	- minor familial dysmorphic feature
Familial retardation		- both parents semi-literate
		- sister ESN/M.

Case 130**Male****IQ 76**

Seen aged 9 years.

Mother aged 21 years, father aged 24 years, at birth. One younger brother. Mother fell downstairs at 36 weeks' gestation - slight bleeding: fetal movements diminished thereafter. Normal delivery at 40 weeks' gestation. BW 3260 gm. No motor, some speech delay. Coordination moderately impaired.

Case 134**Female****IQ 55**

Seen aged 10 years.

Mother aged 27 years, father aged 26 years, at birth. One younger sister. Social class V - father - (divorced) labourer. Hypertension throughout pregnancy. Normal labour at 42 weeks' gestation. BW 2150 gm (<3rd centile). No record of OFC. Mild motor, severe speech delay. Speech very poor when seen. At examination, found to have flat occiput, shallow orbits. Height and weight just below 50th centile, but OFC well below 3rd centile at 47.4 cm - diagnosed as microcephalic. Coordination impaired.

Medical

known risk factors
other factors

- microcephaly
- toxemia
- low birth weight
- incoordination
- *father ESN/M*
- *mother semi-literate*
- *sister ESN/M.*

Familial retardation**Case 135****Male****IQ 74**

Seen aged 10 years.

Mother aged 21 years, father aged 29 years, at birth. One younger brother. Social class IV - father - railway shunter. Threatened abortion at 12 weeks' gestation. Normal delivery at 40 weeks' gestation. BW 3827 gm. Several cyanotic attacks after birth - in SCBU for 3 days. No motor delay. Speech delay - words

by 2 years, but no sentences until 5 years. No incoordination.

Medical

known risk factors
other factors

- perinatal cyanosis
- threatened abortion
- *mother semi-literate.*

Familial retardation**Case 136****Female****IQ 64**

Seen aged 9 years.

Mother aged 23 years, father aged 22 years, at birth. One older sister. Social class V - father - dustman. Normal pregnancy and labour. BW 3300 gm at 40 weeks' gestation. Apgar score of 6 at 5 minutes - in SCBU for 4 days. No motor, but moderate speech delay. No incoordination.

Medical

known risk factors
other factors

- low Apgar score
- none
- *both parents semi-literate*
- *sister ESN/M.*

Familial retardation**Case 137****Female****IQ 73**

Seen aged 11 years.

Mother aged 36 years, father aged 31 years, at birth. One older sister. Social class III - father - boat builder. Normal pregnancy. Elective Caesarean section (previous mode of delivery) at 40 weeks' gestation. BW 3180 gm. No motor delay. Speech late - no words by age 3, still poor, with much substitution, when seen. R.congenital anterior polar cataract and R.divergent squint treated operatively at 7 years. When seen, >3 dysmorphic features. Medial eyebrow flare, small

palpebral fissures, epicanthic folds, L. eye lower than R., mild micrognathia; simple ears with thick helical rim. No incoordination.

Medical known risk factors - none
other factors - >3 dysmorphic features

Familial retardation - none.

Case 138**Female****IQ 68**

Seen aged 10 years.

Mother aged 21 years, father aged 23 years, at birth. One younger sister. Social class III - father - supervisor shop fitter. Normal pregnancy and labour. BW 2830 gm at 40 weeks' gestation. Blue turn 2 hours after birth - in SCBU 3 days. No motor or speech delay. No incoordination.

Medical known risk factors - neonatal cyanosis
other factors - none

Familial retardation - none.

Case 139**Male****IQ 52**

Seen aged 11 years.

Mother aged 18 years, father aged 23 years, at birth. No siblings. Social class II - father - transport manager. Normal pregnancy; spontaneous, fairly rapid labour at 42 weeks' gestation. Apgar score 6 at 5 minutes - mild birth asphyxia diagnosed - in SCBU 24 hours. Apnoeic attack when 3 weeks old - resuscitation by father took about 20 minutes, thereafter in hospital for 6 weeks. Mildly hypotonic - sat at 10 months, walked at 19 months. Severe speech delay - 1-2

words by age 5 years. Grand mal fits at 8 years, occasional fits since - on Carbamazepine. EEG - (aged 9 years) - paroxysmal disturbance. CT scan - (aged 9 years) - normal. Behaviour problems - poor sleep pattern; disorientated - difficulty in finding his way around school; restless, and emotionally labile. Coordination - not tested, unable to cooperate. This child's IQ had deteriorated. when tested at 6 years old it was 84: at 8 years old 57: at 10 years old 52. Transfer to ESN/S education was being considered.

Medical known risk factors - low Apgar score
- prolonged apnoea at 3 weeks
other factors - epilepsy
- behaviour problems [DSM 312.10]

Familial retardation - none.

Case 140**Female****IQ 73**

Seen aged 11 years.

Mother aged 25 years, father aged 27 years, at birth. One older brother, one younger sister. Social class III - father - heating engineer. Normal pregnancy and labour. BW 2830 gm at 42 weeks' gestation. No neonatal problems. Moderate motor delay - head lag still present at 5 months; crawled 14 months, walked at 2 years. Mild speech delay. No incoordination.

Medical known risk factors - none
 other factors - none
 Familial retardation - none.

Case 141**Female****IQ 60**

Seen aged 7 years.

Mother aged 29 years, father aged 33 years, at birth. Three older brothers. Social class III - father - maintenance engineer in car factory. Normal pregnancy. Fetal distress recorded - delivered by Kielland's forceps. Not in SCBU. No motor delay. Speech delayed with very few words until aged 3 years. Seen by paediatrician at age 1 year, because of poor sleeping pattern, and unexplained screaming attacks. Investigations negative. Two febrile fits - one at 16 months old, second at 28 months old. Persistence of poor sleeping pattern, and hyperactive, difficult, strong-willed behaviour. No fear of heights, or road sense. Poor coordination.

Medical known risk factors - fetal distress
 other factors - behaviour problems [DSM 312.10]
 - febrile fits
 - incoordination
 Familial retardation - none.

Case 142**Female****IQ 66**

Seen aged 11 years.

Mother aged 29 years, father aged 26 years, at birth. One younger sister. Social class III - father - (separated) deep sea diver. Toxaemia; induced at 40 weeks' gestation, low forceps delivery. BW 3798 gm. Early development normal, until aged 3 years, then regressed. Difficult, uncooperative behaviour - under psychiatrist. No speech problems. No incoordination.

Medical known risk factors - none
 other factors - toxæmia
 - behaviour problems [DSM 312.10]
 Familial retardation - none
 Poor home circumstances - mother expressed little rapport or empathy with the child.

Case 143**Female****IQ 71**

Seen aged 12 years.

Mother aged 24 years, father aged 27 years, at birth. One older brother. Social class IV - father - van-driver. Repeated bleeding from 2nd to 4th month of pregnancy, occasionally thereafter. Severe toxæmia - induced at 38 weeks' gestation. Breech delivery with forceps; blue and limp at birth. In SCBU for 3 days. BW 2530 gm (<10th centile). No motor delay: speech - mild delay, spoke at 3 years. Seen at hospital aged 6 years, because of tremor. Minimal cerebral damage diagnosed - possibly due to stormy pregnancy. Tall, thin girl with Marfanoid features. Speech somewhat inarticulate. No incoordination or tremor.

Medical known risk factors - blue/limp at birth
 other factors - threatened abortion
 - toxæmia
 Familial retardation - 1 brother ESN/M.

Case 144**Male****IQ 84**

Seen aged 8 years.

Mother aged 35 years, father aged 38 years, at birth. Younger of 2 male siblings. Social class III - father - sheet metal worker. Hyperemesis in first 6 months of pregnancy. Toxaemia - induced at 40 weeks' gestation. Fetal distress recorded - high forceps delivery. BW 3835 gm. Home when 5 days old, returned 2 days later because of weight loss. No motor or speech delay. Large child, with height, weight, and OFC all >97th centile. (Father - large build). No incoordination.

Medical known risk factors - fetal distress
other factors - hyperemesis
- toxaemia

Familial retardation

- none.

Case 145**Female****IQ 59**

Seen aged 9 years.

Mother aged 23 years, father aged 26 years, at birth. Social class V - father - (divorced) labourer. Normal pregnancy. Labour induced at 40 weeks' gestation. BW 3200 gm. Cyanotic turns after birth. Mild motor and speech delay. No incoordination.

Medical known risk factors - neonatal cyanosis
other factors - none

Familial retardation

- father illiterate.

Case 146**Male****IQ 71**

Seen aged 11 years.

Mother aged 33 years, father aged 26 years, at birth. Third of 4 siblings: 2 boys, 2 girls. Social class III - father - cafe owner. Normal pregnancy and labour. BW 2940 gm at 40 weeks' gestation. No motor or speech delay. No incoordination. Frontal upsweep of hair, mild clinodactyly, but no other dysmorphic features.

Medical known risk factors - none
other factors - none

Familial retardation

- none.

Case 147**Male****IQ 80**

Seen aged 9 years.

Mother aged 27 years, father aged 31 years, at birth. One younger sister. Social class III - father - merchant seaman. Bleeding between 3rd and 4th month of pregnancy. Labour induced at 41 weeks' gestation - fetal distress recorded, high forceps delivery. BW 3780 gm. No motor, mild speech delay. Skull and facial asymmetry; short spatulate fingers; bilateral clinodactyly; small nails of both 5th digits, syndactyly toes 2-3, both feet. Poor coordination - could not hop or do heel - toe walking.

Medical known risk factors - fetal distress
other factors - threatened abortion
- >3 dysmorphic features

Familial retardation

- incoordination
- *none.*

Case 148**Male****IQ 63**

Seen aged 11 years.

Mother aged 24 years, father aged 28 years, at birth. One older brother. Social class IV - father - machinist in factory. Normal pregnancy. Spontaneous delivery at 37 weeks' gestation; Apgar score 5 at 5 minutes. BW 2600 gm. In SCBU for 8 days. Seen at 13 months - hypertonic, increased reflexes in arms and legs. OFC just below 5th centile. Hypertonia diminished by 28 months. Scoliosis noted at 44 months, resolved spontaneously. Walked aged 3 years - no undue speech delay. R. hydronephrosis at 9 years - stricture of R. pelvi-uretic junction corrected. When seen, mild spasticity, especially of legs, walked with both feet inturned and heels slightly off the floor. Marked skull asymmetry, with prominence of R. frontal region: OFC 56.4 cm (>97th centile). Simple ears, prominent helical rim. High palate. Arachnodactyly, mild scoliosis. Fine lateral nystagmus. Mild incoordination. of heel - toe walking only.

Medical

known risk factors
other factors

- Apgar score 5
- >3 dysmorphic features
- mild spasticity
- *none.*

Familial retardation**Case 149****Male****IQ 69**

Seen aged 11 years.

Mother aged 26 years, father aged 27 years, at birth. One older sister. Social class III - father - merchant seaman (steward). Mother found to have syphilis at 12 weeks' gestation - treated with penicillin; blood remained positive. Induced at 40 weeks' gestation, normal delivery. BW 3685 gm. Maternal transferred antibodies only present in blood at birth - fluorescent treponemal antibody test - IgG +ve IgM -ve. No motor or speech delay. Bat ears, skull and mild facial asymmetry when seen - 9 whorls on fingers. No incoordination.

Medical

known risk factors
other factors

- intrauterine syphilitic infection
- minor dysmorphic features
- *none.*

Familial retardation**Case 150****Female****IQ 60**

Seen aged 8 years.

Mother aged 28 years, father aged 30 years, at birth. One younger brother. Social class III - father - HGV driver. Hyperemesis in pregnancy - took Debendox until 7th month of gestation. Caesarean section for breech presentation at 42 weeks' gestation. Fetal distress recorded. BW 3713 gm. In SCBU for 1 day. Mild motor delay - sat at 1 year, walked at 18 months. Speech delay - no words before 2 years. Bizarre movements of head, arms and legs noticed in infancy and early childhood - thyroid function, amino acid metabolism and chromosomes checked when aged 3 years - all normal. Behavioural disturbance - unpredictable, difficult to control. When seen, facial features slightly coarse,

obese, large head - height on 25th centile, weight over 75th centile, OFC on 90th centile. Poor coordination - unable to hop or heel - toe walk.

- Medical**
- | | |
|--------------------|--------------------------------------|
| known risk factors | - fetal distress |
| other factors | - hyperemesis |
| | - Debendox medication |
| | - behaviour disturbance [DSM 312.10] |
| | - incoordination |
- Familial retardation**
- both parents of average intelligence or above;
 - brother ESN/S, with similar behaviour problems.

Case 151**Male****IQ 71**

Seen aged 10 years.

Mother aged 26 years, father aged 40 years, at birth. Youngest of 4 male siblings. Social class IV - father - assembly line worker in car factory. Mild toxæmia. Labour induced at 40 weeks' gestation. Low forceps delivery - BW - 2730 gm. OFC 33 cm. Frequent twitching and vomiting recorded in 1st week of life. Referred to hospital with clicking hip aged 1 month: noted to have large head - OFC 42.5cm. Ventriculogram showed large cisterna magna and generalised ventricular dilatation. Hydrocephalus treated with Spritz-Holzer valve; catheter lengthened several times since, still in situ when seen. OFC 9 months after valve insertion was 47.5cm. No motor or speech delay. L.high tone hearing loss. Height, weight and OFC all just >50th centile when seen. No incoordination.

- Medical**
- | | |
|--------------------|----------------------|
| known risk factors | - hydrocephalus |
| | - neonatal twitching |
| other factors | - toxæmia |
- Familial retardation**
- none.

Case 152**Male****IQ 71**

Seen aged 10 years.

Mother aged 20 years, father aged 21 years, at birth. Second of 4 siblings: 3 boys, 1 girl. Social class III - father - HGV driver. Severe hyperemesis - treated with Debendox. Spontaneous delivery at 39 weeks' gestation. BW 2960 gm. No motor or speech delay. Fell from upper window aged 18 months - unconscious for 3 hours, blind for 1 week. Fractured occiput, but no localising signs. In hospital for 2 weeks; no fits. No incoordination.

- Medical**
- | | |
|--------------------|------------------------------|
| known risk factors | - none |
| other factors | - hyperemesis |
| | - Debendox medication |
| | - head injury aged 18 months |

- Familial retardation**
- father ESN/H
 - mother semi-literate
 - 2 brothers receiving remedial help at normal school.

Case 153**Male****IQ 73**

Seen aged 9 years.

Mother aged 19 years, father aged 20 years, at birth. One older sister, one younger maternal half-sister. Social class V - father - labourer. Normal pregnancy, spontaneous labour at 39 weeks' gestation. BW 2640 gm (<10th centile). Apgar score of 2 at 5 minutes, 6 at 10 minutes. In SCBU for 3 days, slightly floppy. Prolonged neonatal jaundice - maximum bilirubin 20 mg/l. No motor delay: speech - delay in forming sentences. No incoordination.

Medical known risk factors - low Apgar score
 other factors - neonatal jaundice

Familial retardation - none.

Case 154**Male****IQ 61**

Seen aged 9 years.

Mother aged 26 years, father aged 29 years, at birth. No siblings. Social class III - father - policeman. Severe urinary tract infection at 6 months gestation. Mild hydramnios. Spontaneous delivery at 39 weeks' gestation. BW 3520 gm. Noted to have broad thumbs at birth - Rubenstein-Taybi syndrome diagnosed. Neonatal jaundice - maximum bilirubin 18 mg/l. Sat at 1 year, walked at 17 months. Bilateral orchidopexy aged 4 years. Speech slow, still poor when seen. Features of Rubenstein-Taybi syndrome - beaked nose, with nasal septum extending below nares; down-slanting palpebral fissures; broad thumbs, with radial deviation of the proximal inter-phalangeal joints. Heavy build, with height on 10th centile, weight on 75th centile; OFC on 25th centile. Poor coordination.

Medical known risk factors - Rubenstein-Taybi syndrome
 other factors - neonatal jaundice

Familial retardation - incoordination

- none.

Case 155**Male****IQ 65**

Seen aged 10 years.

Mother aged 32 years, father aged 25 years, at birth. Two older maternal half-siblings: 1 boy, 1 girl; 2 full siblings: 1 older brother, 1 younger sister. Social class III - father - HGV driver. Normal pregnancy. Spontaneous delivery at 34 weeks' gestation. BW 2620 gm. Apgar score 6 at 5 minutes, OFC 34 cm. Poor muscle tone, feeding problems - respiratory distress syndrome, with R. lower lobe pneumonia. Jaundice - maximum bilirubin 14.4 mg/l. In SCBU for 4 weeks. When seen 3 weeks later, OFC >97th centile, and hydrocephalus was diagnosed. This was treated conservatively; at age 7 months his OFC was 48.25 cm, at age 3 years 53 cm. Mild motor delay: moderate speech delay. Long, narrow face, with OFC, when seen of 59.2 cm (>+2 SD). Normal thumbs. No incoordination.

Medical known risk factors - hydrocephalus
 - low Apgar score
 other factors - neonatal jaundice

Familial retardation - none.

Case 156**Male****IQ 67**

Seen aged 11 years.

Mother aged 36 years, father aged 34 years, at birth. One older sister. Social class III - father - motor mechanic. Normal pregnancy. Elective Caesarean section at 40 weeks' gestation. BW 3175 gm. Apgar score of 6 at 5 minutes. In SCBU for 2 days. Mild motor and speech delay. Incoordination - finger-thumb apposition, heel-toe walking, and hopping. Fine lateral nystagmus.

Medical

known risk factors

- low Apgar score

other factors

- incoordination

Familial retardation

- father semi-literate

Poor home circumstances

- mother very depressed, 2 suicidal attempts, lived at home, but kept to her bedroom. Children cared for by father. Not seen at home interview.

Case 157**Male****IQ 84**

Seen aged 9 years.

Mother aged 26 years, father aged 28 years, at birth. One older brother. Social class III - father - HGV driver. Mother diabetic - diagnosed aged 12 years, well controlled on insulin. Normal pregnancy and labour. BW 2470 gm at 38 weeks' gestation. No motor or speech delay. No incoordination.

Medical

known risk factors

- none

other factors

- maternal diabetes

Familial retardation

- brother also ESN/M.

Case 158**Female****IQ 66**

Seen aged 8 years.

Mother aged 26 years, father aged 27 years, at birth. Youngest of 4 siblings: 3 girls, 1 boy. Social class IV - father - industrial welder. Normal pregnancy and labour. Home delivery. BW 3515 gm at 40 weeks' gestation. No speech or motor delay. No incoordination.

Medical

known risk factors

- none

other factors

- none

Familial retardation

- both parents semi-literate

- 1 brother ESN/M.

Case 159**Female****IQ 66**

Seen aged 10 years.

Mother aged 25 years, father aged 30 years, at birth. Three older maternal male half-siblings,; one younger brother [160]. Social class IV - father - factory assembly worker. Normal pregnancy: high forceps delivery. BW 3090 gm at 40 weeks' gestation. Some motor delay - sat at 10 months, walked at 20 months. Speech also delayed, but stringing words together by 3 years. No incoordination.

Medical

known risk factors

- none

other factors

- none

Familial retardation

- father barely literate

- brother ESN/M [160].

Case 160**Male****IQ 72**

Seen aged 9 years.

Mother aged 26 years, father aged 31 years, at birth. Three older male maternal half-siblings, 1 older sister [159]. Social class IV - father - factory assembly line worker. Influenza and vaginal bleeding at 4 weeks' gestation. Normal delivery at 41 weeks' gestation: BW 3140 gm. No motor or speech delay. No incoordination.

Medical

known risk factors

- none

other factors

- threatened abortion

Familial retardation- *father barely literate*- *sister ESN/M [159].***Case 161****Male****IQ 70**

Seen aged 9 years.

Mother aged 38 years, father aged 53 years, at birth. Youngest of 10 siblings: 7 boys, 3 girls. Social class III - father - railway worker - head shunter. Toxaemia in pregnancy - induced at 38 weeks' gestation. Difficult labour - Kielland's forceps rotation, but no recording of fetal distress, Apgar score 8 at 5 minutes, BW 4330 gm (90th centile). No motor or speech delay. Obese - when seen, OFC on 50th centile, height just over 50th centile, weight >97th centile. No incoordination.

Medical

known risk factors

- none

other factors

- toxaemia

Familial retardation- *none.***Case 162****Male****IQ 64**

Seen aged 11 years.

Mother aged 19 years, father aged 20 years, at birth. Older of 2 brothers. Social class IV - father - post-office worker. Normal pregnancy and labour. Some motor and speech delay. Walked at 27 months, spoke phrases at 3 years. No incoordination.

Medical

known risk factors

- none

other factors

- none

Familial retardation- *mother ESN/M.***Case 163****Female****IQ 63**

Seen aged 12 years.

Mother aged 23 years, father aged 31 years, at birth. One older brother. Social class III - father - builder. Normal pregnancy and labour. BW 3175 gm. No motor or speech delay. Family lived in Spain when proband aged 6-10 years - home correspondence education. No incoordination.

Medical

known risk factors

- none

other factors

- none

Familial retardation- *none.*

Case 164**Female****IQ 80**

Seen aged 7 years.

Mother aged 29 years, father aged 27 years, at birth. One older sister. Social class III - father - coach builder. Hyperemesis for 1st 6 months of pregnancy - no medication, Normal delivery at 40 weeks' gestation. BW 3628 gm. No early motor or speech delay. Encephalitis aged 3 years - in hospital for 3 weeks. No virus isolated. Has since had about 1 grand mal fit per month - on sodium valproate. Behaviour, both at school and home, very disruptive, frequent spells of short term care; thought to be gradually improving. Well coordinated, apart from heel-toe walking.

Medical known risk factors - encephalitis aged 3 years
 other factors - hyperemesis
 - epilepsy
 - severe behaviour disturbance [DSM 312.10]
Familial retardation - none.

Case 165**Male****IQ 69**

Seen aged 10 years.

Mother aged 24 years, father aged 30 years, at birth. One younger brother. Social class III - father - electrician. Normal pregnancy and labour. BW 3486 gm at 42 weeks' gestation. Some motor delay - walked at 25 months, also speech delay; some phrases by aged 3 years. Coordination - fair.

Medical known risk factors - none
 other factors - none
Familial retardation - none.

Case 166**Female****IQ 62**

Seen aged 11 years.

Mother aged 27 years, father aged 28 years, at birth. Youngest of 4 siblings: 2 boys, 2 girls. Social class V - father - casual labourer. Normal pregnancy. Spontaneous labour at 36 weeks' gestation, normal delivery. BW 2680 gm. Neonatal cyanosis - breathing difficulties in 1st 3 days of life. Nursed in incubator. No motor or speech delay. No incoordination.

Medical known risk factors - neonatal cyanosis
 other factors - premature birth
Familial retardation - *both parents semi-literate*
 - *1 brother ESN/M.*

Case 167**Female****IQ 70**

Seen aged 11 years.

Mother aged 29 years, father aged 34 years, at birth. One older brother. Social class IV - father - electrician's mate. Normal pregnancy and labour. BW 4550 gm (>97th centile) at 41 weeks' gestation. No motor or speech delay. Hospital investigation at age 1 year for persistent vomiting; blood urea, electrolytes, amino-acid chromatography, IVP, all normal. Intermittent cyclical vomiting and constipation since. No incoordination. L. internal squint (operated at 3 years) -

and poor coordination of eye movements.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- none.

Case 168

Male

IQ 70

Seen aged 11 years.

Both parents aged 35 years, at birth. Three older sisters.; Social class III - father - (divorced) fork lift truck driver. Normal pregnancy and labour. BW 3840 gm at 40 weeks' gestation. No motor or speech delay. No incoordination.

Medical	known risk factors	- none
	other factors	- none
Familial retardation		- none.

Case 169

Male

IQ 80

Seen aged 9 years.

Mother aged 30 years, father aged 31 years, at birth. One younger sister. Social class II - father - bank manager. Hyperemesis; appendicectomy when 18 weeks pregnant, followed by wound abscess - treated with ampicillin. Toxaemia - with induction at 39 weeks' gestation for hypertension. Face presentation - Kielland's rotation. BW 2660 gm (<10th centile). Not in SCBU. No motor, some speech delay.

Seen by paediatrician at 31 months because of lack of speech development - not putting words together. Height and OFC noted then to be below 3rd centile; bone age of 15 months. Bone age at 8 years, 9 months equivalent to 5 years. When seen - height below 3rd centile, weight on 3rd centile, OFC on 25th centile. Appearance not dysmorphic; R.single palmar crease. No incoordination.

Medical	known risk factors	- none
	other factors	- hyperemesis
		- appendicitis in pregnancy
		- toxaemia
		- small stature
Familial retardation		- none

APPENDIX B

THE UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

PROFESSOR OF CHILD HEALTH

J. NORMAND, D.M., F.R.C.P.



CENTRE BLOCK, ROOM CG56,
SOUTHAMPTON GENERAL HOSPITAL,
TREMONA ROAD,
SOUTHAMPTON, SO9 4XY.

Telephone: 777222, ext. 4337

Dear Doctor

With the help of a research grant from the Wessex Regional Health Authority and with the permission of the Hampshire Education Authority we are investigating the causes of mental handicap in children attending schools for the mildly mentally handicapped (ESN(M)) in Southampton. The study involves interviewing the mother or both parents, examining the child at school, and, if consent is granted, taking blood and urine samples from mother and child.

Your patient attending School has been ascertained as an index patient. If for any reason you think it inadvisable to include this child in the study, please let us know, otherwise we will write to the mother to arrange a home visit in the next few weeks.

We will send you a note of our findings for your records as soon as the results are complete.

Yours sincerely,

N.R. Dennis, MB, MRCP
Senior Lecturer in Clinical Genetics

Margaret A. Lamont, MB, ChB
Research Assistant

THE UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

PROFESSOR OF CHILD HEALTH
S. NORMAND, D.M., F.R.C.P.



CENTRE BLOCK, ROOM CG56,
SOUTHAMPTON GENERAL HOSPITAL,
TREMONA ROAD,
SOUTHAMPTON, SO9 4XY.

Telephone: 777222, ext. 4337

Dear

We are making a study of children in Southampton who are attending certain types of special schools. This is being done with the consent of the Education Authority. The aim is to find out more about the causes of learning difficulties in these children. We should like, if you are agreeable, to include in this study.

One of us, (Dr. Lamont), will call on you to explain what sort of information we hope to collect. You can then decide whether or not you wish to be included.

If we do not hear from you, Dr. Lamont will call around on . If this time is not convenient and you would like to arrange a different time, please telephone the above number.

If you do not wish to take part in the study and do not want anyone to call, please telephone or write to us at the above address to let us know.

Yours sincerely,

(Dr.) N.R. Dennis

(Dr.) Margaret Lamont

NAME:

Date of Birth:

<u>HISTORY:</u>	<u>School Record</u>	<u>Hospital Record</u>	<u>Parents</u>
Birth weight			
Gestation			
Pregnancy			
Drugs			
Labour			
Apgar - 5 mins.			
Neonatal problems			
Age at discharge			
<u>Skills:</u>			
Sitting up			
Walking			
Meaningful words			
Potty training			
<u>Tests:</u>			
Hospital			
Investigations			
Seizures/blackouts			
Concussions			
Wears glasses	Date: R L		
Wears glasses	R L		
Quintessence			
:	Date: Sweep test		
Speech therapy			
<u>HISTORY:</u>			
General health			
Signs			
Toxic features			
Relevant circumstances			
Parents' opinion:			

_____ Date of Interview: _____

. _____
I. _____
II. _____

gs:

ame:	Date of birth	B.W.	Gestn.	Preg.	Neonatal	Develop	Educat.	Medical
_____	_____	_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____	_____	_____

me:	Date of birth	Occupation	Education	Medical
_____	_____	_____	_____	_____

me (maiden):	Date of birth	Occupation (inc. past)	Education	Medical
_____	_____	_____	_____	_____

relatives:

Circumstances:

her's rating: Superior/average/lower/dull/ESN
her's rating: Superior/average/lower/dull/ESN
e: Superior/average/lower/dull/ESN

mission for examination: YES/NO Blood/Urine YES/NO

her's urine: YES/NO Blood: YES/NO

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PROFESSOR OF CHILD HEALTH
I.C.S. NORMAND, D.M., F.R.C.P.

CENTRE BLOCK, ROOM CG56,
SOUTHAMPTON GENERAL HOSPITAL,
TREMONA ROAD,
SOUTHAMPTON, SO9 4XY.

Telephone: 777222, ext. 4337

I, _____, consent to the medical
examination of my son
daughter

for the purpose of a study of children with special educational needs.

Signed: _____ Father
Mother

I also consent to the taking and testing of blood and urine samples from _____ as part of the investigation.

Signed: _____ Father
Mother

THE UNIVERSITY OF SOUTHAMPTON

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PROFESSOR OF CHILD HEALTH

M. NORMAND, D.M., F.R.C.P.



CENTRE BLOCK, ROOM CG56,
SOUTHAMPTON GENERAL HOSPITAL,
TREMONA ROAD,
SOUTHAMPTON, SO9 4XY.

Telephone: 777222, ext. 4337

Dear Sir,

We are anxious to trace the labour records of children
attending ESN(M) schools in Southampton.

Mrs. _____, date of birth _____
was delivered on _____ at _____
I should be most grateful if you could supply the following details:

Pregnancy - illness, adverse features

Gestation:

Labour:

Birth weight:

Apgar score at 5 mins:

Neonatal problems:

Many thanks for your help.

Yours sincerely,

M. A. Lamont

M.A. Lamont
Research Registrar

The Medical Records Officer,

PHYSICAL EXAMINATION

Date: _____

Name: _____ Sex: _____ Date of Birth: _____

Racial Origin: _____ Height: _____ Weight: _____

General appearance: _____ Build: _____

Head shape: _____ Hair pattern: _____ O.F.C. _____

Face: (general)

Eyes - Outer canthi _____ Inner canthi _____

Strabismus _____ Nystagmus _____

Fundi _____

Nose - Bridge _____ Shape _____ Nares _____

Maxilla _____ Mandible _____

Philtrum _____ Mouth _____ Lips _____

Palate _____ Teeth _____

Ears - position _____ Form _____

Upper limbs:

Joint mobility - wrist _____ McP _____ Elbow _____

Hands - nails _____ Creases: R _____

digits _____ L _____

Lower limbs:

Joint mobility _____ Ankle _____ Knee _____

Feet _____ Toes _____ Creases _____

Genitalia - rashes: _____ Hair growth _____

Pigmentation _____ Elasticity _____

Spine:

Scoliosis

Kyphosis

Lordosis

Neck

Hair line

Sternum

Nipples

Heart Sounds:

Abdomen:

Liver

Spleen

Herniae

Genitalia

Testes

Central Nervous System:

Reflexes -

R

L

Knee

Ankle

Plantar

Speech

Gait

Coordination:

Hand tapping

Finger/thumb

Heel/toe

Finger/nose

Hopping

Photograph:

YES/NO

Blood:

YES/NO

THE UNIVERSITY OF SOUTHAMPTON

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PROFESSOR OF CHILD HEALTH
J.S. NORMAND, D.M., F.R.C.P.



CENTRE BLOCK, ROOM CG56,
SOUTHAMPTON GENERAL HOSPITAL,
TREMONA ROAD,
SOUTHAMPTON, SO9 4XY.

Telephone: 777222, ext. 4337

Dear

re:

Some time ago, we wrote to you about the possibility of including this patient in a survey of ESN/M children.

The following tests were done as part of the survey and we give you the results:

Chromosomal analysis
TSH, amino acid chromatography

Comment:

Many thanks for your help.

Yours sincerely,

M.A. Lamont
Research Registrar

THE UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

PROFESSOR OF CHILD HEALTH

D.S. NORMAND, D.M., F.R.C.P.



CENTRE BLOCK, ROOM CG56,
SOUTHAMPTON GENERAL HOSPITAL,
TREMONA ROAD,
SOUTHAMPTON, SO9 4XY.

Telephone: 777222, ext. 4337

Dear

You very kindly cooperated in our recent survey of children at
_____ school, and wished to know results of the tests we did for
_____.

These results are now available and have shown nothing abnormal;
we have sent a detailed copy of the results to your family doctor.

Many thanks for your help.

Yours sincerely,

M.A. Lamont
Research Registrar

APPENDIX C

LAMONT, M.A.
M.D. 1992

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Chromosome abnormalities in pupils attending ESN/M schools

M A LAMONT, N R DENNIS, AND M SEABRIGHT



Chromosome abnormalities in pupils attending ESN/M schools

M A LAMONT, N R DENNIS, AND M SEABRIGHT

Department of Child Health, Southampton General Hospital, and Wessex Regional Cytogenetics Unit, Salisbury General Hospital

SUMMARY One hundred and sixty six children attending educationally subnormal/mild (ESN/M) schools were karyotyped as part of a project investigating the aetiology of mild mental retardation. Nine had significant chromosome abnormalities. Five of six children identified during the survey had no dysmorphic features—47,XXY (two), 48,XXYY, 46,XX 15q–, and 46,XX,t(X;19). One dysmorphic boy had a balanced translocation—46,XY,t(3;15). Three were already known—47,XX+21 (two) and 46,XY, 14q+.

We suggest that routine karyotyping of children with mild mental retardation be considered.

Chromosome abnormalities are known to be an important cause of severe mental retardation. They account for over a third of all those with an IQ of <50, with trisomy 21 predominating.¹ The contribution of chromosome abnormalities to mild mental handicap (IQ 50–70) has not been so well defined, possibly because mild mental handicap is not always readily apparent. Its expression may be limited to poor scholastic performance, with affected individuals not being easy to identify in pre- or post school years. Nevertheless, surveys of the mildly mentally handicapped have shown a higher prevalence of chromosome abnormalities than exists in the general population.^{2–4} Chromosome analysis in these surveys was limited to those mildly retarded children with dysmorphic features or abnormal buccal smears. We report here on chromosomal analyses of unselected children attending educationally subnormal/mild (ESN/M) schools in Southampton performed as part of a project investigating the aetiology of mild mental handicap.

In addition to routine chromosome studies we wished to ascertain the prevalence of the fragile X chromosome in this group of ESN/M children. The association of the fragile X marker in boys with mental retardation, both severe and mild, has been recognised over the last few years.^{5–7} Turner found fragile X chromosomes in five out of 72 mildly retarded girls with no physical abnormalities, and recommended testing for fragile X chromosome in mildly retarded girls.⁷

Materials and methods

Population. ESN/M schools provide special education for children who come into the range of mild mental handicap, defined by the World Health Organisation in 1968 as IQ 50–70. Intelligence tests are usually carried out only in children who have been perceived to fail academically and are being considered for ESN/M schools. Factors other than IQ may influence referral of a child to an ESN/M school. Social adaptation, parental attitudes, and the availability of remedial teaching in the 'normal' school can all bias selection. Thus a study population of children attending ESN/M schools is unlikely to contain all school children in the IQ range 50–70, nor is it unbiased.

Within these limitations, we thought that a survey of children attending ESN/M schools was a valid project and the only practicable way to identify a study population of mildly mentally handicapped children.

Methods. Chromosome analysis was performed as part of a wider survey. Information collected for each child also included details of pre- and perinatal history and early development. A subjective assessment was made of the social conditions at home and parental ability; these were classed as superior, average, or poor.

With the written permission of parents, the children had a detailed clinical examination at

Table Major chromosome abnormalities, with other features, in 9 out of 166 children from ESN/M schools

Case No	Karyotype	IQ	Maternal age at birth	Paternal age at birth	Birth weight (g)	Factors in pregnancy	Perinatal factors	Early motor delay	Early speech delay	Dysmorphic features	Home background	Other features
1	47,XX+21	64	38	43	3373	—	—	—	+	Down's syndrome	Average	—
2	47,XX+21	74	46	52	3040	Mild hypertension	—	—	—	Down's syndrome	Average	—
3	46,XY dup.14 (q21-q22)	69	20	33	3146	—	Jaundice	+	+	Microphthalmos short digits. Simian crease	Average	Mother - 46,XX. Father - 46,XY. Hirschsprung's disease - 1 year
4	47,XXY	72	24	20	3800	—	—	—	+	—	Poor	—
5	47,XXY	76	38	46	2182	Hypertension. Placental insufficiency	Birth asphyxia	—	+	—	Poor	Mentally retarded brother
6	48,XXYY	68	25	27	3061	—	—	—	+	Mild bilateral clinodactyly. Shield chest	Average	Behaviour problems
7	46,Xt(X;19)(p11.2;q13.3)	74	23	29	2353	Excess alcohol intake	—	—	—	—	Poor	Mother - 46,XX. Father - 46,XY
8	46,XX,del 15 (q11.2;q13.1)*	66	39	38	2780	Hypertension	Birth asphyxia	—	—	—	Average	Mother - 46,XX. Father - 46,XY
9	46,XYt(3;15)(p11;q21.2)	48	23	49	2870	—	—	+	+	High narrow palate. Tongue tie. Bilateral clinodactyly	Poor	Epilepsy. Behaviour problems. Mother, grandmother - 46,XXt(3;15)

*Fragile X present in 2 out of 225 cells.

school. Blood samples were obtained and sent by first class post to the Wessex Regional Cytogenetics Unit. Cultures were set up in low folate Iscove medium and harvested at 48 or 72 hours. Thirty metaphases from G banded preparations were examined from each child.

A repeat analysis was done on children karyotyped previously to screen them for the presence of the fragile X chromosome.

Parents' chromosomes were analysed when a possible familial abnormality was found.

Results

From a total population in Southampton of 11 921 children born between August 1971 and July 1976, 229 (2%) were attending ESN/M schools during the period of the survey. Parental permission for inclusion in the survey was obtained for 169. Chromosome results are available in 166 children, 96 boys and 70 girls. In one child venepuncture was unsuccessful on two occasions. A repeat sample was not obtained in two children out of eight in whom the initial culture failed.

Nine children (5%) had significant chromosomal abnormalities. Details are given in the Table. The two girls with Down's syndrome and a dysmorphic boy, karyotype 46,XY,14q+, had already been identified. The girl 46,XX,del(15) had one cell with fragile X in a repeat culture performed to check on the autosomal deletion. A further culture, incubated with uracil, and caffeine plus uracil, showed fragile X in two cells out of 225 examined.

Discussion

Children with evident dysmorphic features and developmental delay will usually be seen at an early age for paediatric assessment, which may include cytogenetic analysis. Mild developmental delay occurring in children without overt clinical features, however, is not usually considered to be an indication for chromosomal investigation. Such children may progress reasonably well in preschool years and are often referred for special education after a period in normal schools, when their difficulty in coping becomes apparent. Attention is then directed towards providing education suited to the child's needs, and, without specific indication, no detailed medical investigation is undertaken. Perinatal problems or a poor social background may be accepted as sufficient aetiology.

Of the 166 children in this survey, nine (5%) had a major chromosome anomaly. This is a 10-fold increase over the incidence of chromosome abnormalities found, with less sophisticated cytogenetic

techniques, in newborn infants.⁹ If we had limited chromosomal analysis in this survey to children with dysmorphic features, or to children with no adverse features in their early background, we should have failed to identify four. In five of the six children identified during the study there was no indication for chromosomal analysis other than mild mental retardation; they were not noticeably dysmorphic. In addition, four of these five had adverse factors in pregnancy, the perinatal period, or in their social background. Ironically, the one dysmorphic child—46,XY,t(3;15)—in whom a chromosome abnormality was found had inherited the translocation from his phenotypically normal mother and maternal grandmother. It is therefore likely to be balanced and unassociated with his retardation or dysmorphic features.

Sex chromosome anomalies were found in three of the 96 boys (3%): two 47,XXY, one 48,XXYY. All three showed the speech problems commonly found in boys with sex chromosome aneuploidy.⁹ Sex chromosome abnormalities occur in 0.3% of newborn boys.¹⁰ The total school population of appropriate age in Southampton during the period of the survey was 11 921. Of these children, about 18 boys should have an abnormal sex chromosome complement. We identified three. A follow up study of 12 boys aged 16–18 years found to have XXY karyotypes during a neonatal screening programme reported that they had no difficulties with education until secondary school.¹¹ It is therefore possible that problems in the early history and family background were the main factors responsible for the early referral to an ESN/M school of the two XXY boys identified in the survey.

The XXYY boy had no adverse features in his history or social environment. The mean IQ of 33 XXYY boys reviewed by Barlow was 62.6;¹² the retardation of our XXYY boy can be reasonably attributed to his sex chromosome aneuploidy. He had poor coordination, a short attention span, and impulsive behaviour, which are in keeping with other recorded XXYY boys.¹³

The girl with karyotype 46,X,t(X;19) fell within the range of borderline intelligence—IQ 74. Mental retardation is not invariable with X autosome translocations but was present in six out of 66 cases reviewed.¹⁴ Despite a history of very heavy alcohol intake by her mother during pregnancy, she showed none of the physical signs of the fetal alcohol syndrome, but one cannot exclude this as a contributory factor in her retardation.

The deletion of chromosome 15 found in one child is similar to that described in association with the Prader-Willi syndrome.¹⁵ This girl had, apart from her retardation, no features of the syndrome. She

had an Apgar score of 4 at five minutes after delivery and was in the special care nursery for a week thereafter, but there was no history of hypotonia or motor developmental delay. She was heavily built, but not unduly obese, and did not have an exceptional appetite. Schwartz reviewed 15 cases with similar deletions of 15q; while 13 of these were hypotonic, the only feature common to all was mental retardation.¹⁶ This girl's retardation is probably due, at least in part, to the chromosomal deletion.

Fragile X chromosome in one out of 166 children in this study does not reflect the prevalence of fragile X found in other studies of ESN/M children. Blomquist, having found the fragile X chromosome in five out of 110 mildly mentally retarded boys, concluded that, next to trisomy 21, the fragile X syndrome is the most common single identifiable cause of mild mental retardation in boys.¹⁷ Hecht recommends that 50 cells, 10 banded, 40 unbanded, should be checked to detect the presence of fragile X.¹⁸ In this study 30 cells were examined from each specimen. This may have reduced the level of detection but is a possible, rather than probable, explanation for the low prevalence of fragile X in these children. The selection policies of different education authorities could affect the prevalence of certain conditions in school children receiving special education.

This study of an unselected series of 166 mildly retarded children has detected a prevalence of chromosome abnormalities of 5%. Only one of these abnormalities, the balanced (3;15) translocation, carried a familial risk. We find, however, that a medical 'label' often helps parents to accept their child's need for special education. We would suggest that consideration be given to karyotyping all children referred to ESN/M schools.

This research was supported by a grant from Wessex Regional Health Authority. We are indebted to Hampshire Education Authority, the head teachers, staff, and parents at the schools involved in the project for their cooperation.

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LAMONT, N.A.
M.D. 1992

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Aetiology of mild mental retardation

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British Medical Association, Tavistock Square, London WC1H 9JR



Aetiology of mild mental retardation

M A LAMONT AND N R DENNIS

Department of Child Health, Southampton General Hospital, Southampton

SUMMARY A clinical and family study was carried out in 169 children attending schools for the mildly mentally retarded in Southampton to assess the prevalence of recognised medical risk factors; 71 children (42%) had such risk factors. These were prenatal in 22, perinatal in 41, and postnatal in eight. Risk factors of possible, but less certain, significance were found in a further 63 children (37%). In 86 families (51%) there was a history of serious educational problems in both parents. The prevalence of both types of risk factor was higher in the children whose parents had no educational problems. There were, however, 25 children (15%) whose parents had no history of educational problems and in whom medical risk factors were either absent or minimal.

The traditional view that mild mental retardation is largely caused by polygenic and sociocultural influences has been challenged by recent studies.¹⁻³ Increasing ability to identify genetic syndromes, chromosome abnormalities, and biochemical defects associated with mental retardation, has extended the scope of diagnosis and the possibility of attributing mental retardation to a specific cause. We therefore undertook a study of children attending schools for the mildly mentally retarded to assess the contribution of medical, and especially genetic, factors of recognised aetiological importance. Medical factors of possible but not fully established relevance were also recorded. We hoped to assess the extent to which mild mental retardation in the local population might be reduced by early diagnosis followed by treatment, genetic counselling, or prenatal diagnosis.

Children identified as having delayed development during preschool years are usually seen by a paediatrician for assessment, but mild mental retardation may not be apparent until after a period in a normal school. Children referred for special education at this stage are not usually referred for a paediatric opinion unless there is a specific indication. We hoped that this study would provide guidelines for the medical investigation of children attending schools for the mildly mentally retarded. Non-medical factors such as parental education and home environment are considered briefly here, but are the subject of another report.⁴

Patients and methods

Schools for the mildly mentally retarded provide education for children with learning difficulties;

there are separate schools for children with physical handicaps. Southampton is well provided with facilities for mildly mentally retarded children. Referral requires parental approval but is otherwise unrestricted. The survey was carried out before the 1983 Education Act which encourages integration of 'less able' pupils into normal schools, and hence children were more readily referred than at present.

The study population was drawn from children aged 7-11 years attending the three Southampton schools that provide education for mildly mentally retarded children. At the time of the study the total school population aged 7-11 years was 11 921, of whom 229 (2%) attended schools for the mildly mentally retarded. One hundred and sixty nine children (93 boys and 79 girls) were included in the study. The parents of 31 children declined to take part and the parents of 19 did not actively refuse, but did not cooperate. Six children who were in foster homes and four who left school in the course of the study were also excluded.

Children referred to schools for the mildly mentally retarded do not always have their intelligence quotient (IQ) tested beforehand. Referral is usually because of an inability to cope with normal education, and IQ assessment by an educational psychologist is secondary. Eighty nine (53%) children in the survey had IQs within the accepted range of mild mental retardation (IQ 50-70).⁵ Seventy five (44%) were of borderline intelligence (IQ 71-85). Five (3%) had not had a formal test. The study was therefore not confined to children with mild mental retardation, but included children of borderline intelligence whose learning problems had been sufficient to merit referral to a special school.

With the cooperation of head teachers and with the knowledge of family doctors, parents of children attending the schools were invited by letter to take part in the survey. Those who agreed were visited at home where a family history was taken and parents were asked about their own medical and educational backgrounds. They were asked for details of pregnancies, and the births, early development, and education of all their children. Blood and urine specimens were taken from the mothers, and written permission was obtained for study children to be seen and tested. School medical records and hospital records were checked for information about the children's medical histories.

At school each study child had a detailed clinical examination that included measurements of height, weight, and cranial circumference, and inspection for minor malformations including abnormal skull shape, unusual facies, abnormal ears, hypertelorism, epicanthic folds, high palate, asymmetric chest, wide spaced nipples, clinodactyly, single palmar crease, abnormal finger creases, minor malformations of fingers and toes, and abnormal dermatoglyphics. Coordination was tested by hand tapping, finger/thumb and finger/nose apposition, heel/toe walking, and hopping. The child's performance in each test was rated as satisfactory or poor.

Poor performance in two or more tests indicated incoordination. The same series of measurements, examination for minor malformations, and coordination tests was carried out on 55 children in the same age range attending normal schools. Blood and urine samples were taken from the study children. All urine samples were screened by standard methods for glucose, protein, blood, ketones, cysteine, cystine, and homocystine. Quantitative amino acid analysis was done on mothers' blood samples with a Rank-Hilger-Chromaspeck amino acid analyser. Blood spot screening for hypothyroidism and phenylketonuria, and chromosome analysis including examination for the fragile (X) chromosome, were done on children's blood samples.

Perinatal factors in index children with no major prenatal or postnatal factors were compared with those of their unaffected siblings (attending normal schools) who acted as paired controls. The control sibling was defined as the one nearest in age to the index patient, and those index patients with no unaffected siblings were left out of the comparison.

Postnatal events were considered significant if the child had been developing normally before the event, but showed developmental delay thereafter.

Results

KNOWN RISK FACTORS

Medical features that probably contributed to the referral were identified in 71 of 169 children (42%). (table 1). Only five children had more than one such feature, and all of these had a combination of prenatal and perinatal features.

Prenatal features

Chromosome abnormalities were present in eight of 22 children with prenatal features. These have been described elsewhere.⁶ Three children—two girls with Down's syndrome, and a boy with karyotype 46,XY,14q+—were known to have a chromosome abnormality before the survey. The others included three boys with sex chromosome aneuploidy—47,XXY (2), and 48,XXYY (1), one girl with an autosomal deletion—46,XX,del(15)(q11.2;q13.1), and one girl with an X-autosome translocation, 46,X,t(X;19). None of these five children had obvious dysmorphic features. Mothers of four children—the two with Down's syndrome, one boy with Klinefelter's syndrome, and the girl with karyotype 46,XX,del(15)—were aged 38 years or over when the children were born.

Two children had 'Mendelian' syndromes; one boy had Sotos' syndrome and his mother also had features suggestive of the syndrome. One boy had

Table 1 Medical features of probable aetiological importance in 71 mildly mentally retarded children

Aetiological feature	No of children
Prenatal:	
Chromosome abnormality	8
Malformation of the central nervous system	5
Infection	2
Sotos' syndrome	1
Aarskog's syndrome	1
Rubenstein-Taybi syndrome	1
Cohen's syndrome	1
Prader-Willi syndrome	1
Alcohol fetopathy	1
Inborn error of metabolism	1
Perinatal:	
Twitching or cyanosis during first week	16*
Apgar score <7 at 5 minutes	16†
Fetal distress	10‡
Blue or limp at birth	4
Postnatal:	
Infection of the central nervous system	3
Apnoea	2
Status epilepticus	1
Intracranial haemorrhage	1
Severe pertussis	1

*Includes two with prenatal signs; †includes three with prenatal features; ‡diagnosed by obstetrician.

Aarskog's syndrome. There was no family history of retardation, but his mother and grandmother were of short stature and had ptosis. Three children had 'non-Mendelian' syndromes associated with mental retardation. One boy had Rubinstein-Taybi syndrome, which had been identified at birth. Two children were identified in the survey; one girl had Cohen's syndrome, and one had Prader-Willi syndrome, without a demonstrable chromosome abnormality. Of three girls with microcephaly, one had minor dysmorphic features that did not fit into any recognised syndrome; the other two had no associated physical features. All three had pronounced incoordination. Two boys had hydrocephalus, one of which had been diagnosed and treated surgically when he was referred for a clicking hip at the age of 4 weeks. The other, born at 34 weeks' gestation, had birth asphyxia and a stormy neonatal course. Hydrocephalus, noted at 7 weeks of age, was not treated surgically.

Two children had had prenatal infections. Toxoplasmosis was diagnosed at the age of 9 months in one child who had severe retinal scarring and intracranial calcification. The mother of one boy had acquired syphilis in the first trimester, and he had antibodies present at birth. One child, with an alcoholic mother, had features of the fetal alcohol syndrome. One other mother admitted to heavy drinking in pregnancy; her child had an X-autosome translocation but no features of fetal alcohol syndrome. Congenital adrenal hyperplasia had been diagnosed in a child at the age of 5 days. This led to a crisis seven weeks later with fitting, opisthotonos, and subsequent facial palsy. The investigations carried out on urine and blood samples did not show any biochemical defects in mothers or children, nor any hypothyroidism in the children.

Perinatal features

Nineteen children had been born outside the South-

ampton district; birth records for nine could not be traced, but the mothers gave no history of perinatal problems. Six children had been born at home; one was admitted to hospital blue and limp shortly after birth, but there was no history of perinatal stress in the other five. Thirty nine children had been born in small peripheral hospitals where Apgar scores were not routinely recorded. Three of these children who were blue and limp at birth and were transferred to special care units have been included in the group with recognised perinatal stress. A history of perinatal stress was the only recognisable risk factor in 41 children. Five children with an adverse perinatal history also had a significant prenatal feature—two children had chromosome abnormalities (47,XXY, 46,XX,del(15)), and one boy with hydrocephalus had low Apgar scores; the other hydrocephalic boy and the child with congenital adrenal hyperplasia had recorded neonatal twitching.

One hundred and twenty study children with no recognisable prenatal or postnatal risk factors had siblings receiving normal schooling. The perinatal features of the study and control groups are shown in table 2. Recordings of fetal distress or low Apgar scores were less than half as common in the control as in the study group. No child in the control group had recorded neonatal twitching or cyanosis. Overall, the incidence of adverse perinatal factors was significantly less in the control group ($p<0.001$).

Postnatal features

Two children had had meningitis, aged 6 and 9 weeks, respectively, and one girl had had encephalitis when she was 3 years old. One boy found cold and limp in his cot when 3 weeks old, and another found apparently lifeless in his pram at 6 months, were regarded as 'rescued cot deaths'. Both these children had behaviour problems. One boy, when aged 18 months developed status epilepticus which took three to four days to come under control; he also had a behaviour disorder. One child developed bilateral subdural haematomas after a non-accidental injury, and she had a residual hemiparesis. The last child in this group was developing normally until he had prolonged pertussis at the age of 2 years. He has since been physically as well as mentally delayed, with small stature and retarded bone age.

POSSIBLE RISK FACTORS

One hundred and six study children had in their history or examination medical features of possible relevance but with no established link with retardation. Forty three of these children also had recog-

Table 2 Perinatal features in 120 mildly mentally retarded children and paired siblings receiving normal education who acted as controls

	No of study children	No of normal children
No adverse feature	87	111
Adverse features:		
Fetal distress	9	3
Apgar score <7 at 5 minutes	11	5
Blue or limp at birth	2	1
Twitching or cyanosis during first week	11	0

nised risk factors. Of 63 children with risk factors of only possible relevance, 37 had just one feature, and 26 more than one (table 3).

Three children had been born to mothers with type I diabetes and in all three this was the only medical factor noted. Insulin control was reasonable—none of the mothers had 'brittle' diabetes. One of the children weighed 4770 g (>97th centile) at birth but there were no problems at delivery; the other two children had birth weights within normal limits. Four children—all boys—had major malformations not affecting the central nervous system; three had cleft lip and palate, one of whom also had Poland's anomaly. The fourth child

had a ventricular septal defect that was successfully repaired when he was 2 years old.

Twenty one survey children were born at or before 36 weeks' gestation, but in none was this the sole feature. Thirty survey children (18%) had heights on or below the third centile. Ten of these children had no other medical feature. Four of 55 control children (7%) had this degree of short stature. Ten children (6%) had cranial circumferences on or above the 97th centile. This was the sole medical finding in four. Two control children (4%) had this degree of macrocephaly. Twenty one children (12%) had severe behaviour problems, all but two of whom had other medical features. Of the

Table 3 Medical features with no well established link with mental retardation in 106 mildly mentally retarded children

<i>Feature</i>	<i>No of times each feature present (n=106)</i>	<i>No of children in whom this was sole medical feature (n=37)</i>	<i>No of times this feature was accompanied by a known risk factor (n=43)</i>	<i>No of times this feature was accompanied by one or more other feature (n=26)</i>	
				<i>One</i>	<i>More than one</i>
Prenatal:					
Twinning	9	0	2	2	5
Chromosome translocation	1	0	0	0	1
Maternal diabetes	3	3	0	0	0
Maternal drug taking	6	0	2	2	2
Maternal operation	1	0	0	0	1
Maternal injury	2	1	0	1	0
Threatened abortion	8	1	4	2	1
Hyperemesis	14	2	7	3	2
Maternal toxæmia	14	4	9	0	1
Maternal anaemia	5	0	1	0	4
Small for gestational age	11	1	5	2	3
Major malformation	4	1	2	0	1
Perinatal:					
Gestation <37 weeks	21	0	11	2	8
Antepartum bleeding	4	1	0	1	2
Rapid delivery	3	1	1	0	1
Neonatal jaundice	10	0	7	0	3
Excessive weight loss	1	0	0	0	1
Postnatal:					
Severe malnutrition	2	0	1	0	1
Immunisation reaction	1	0	0	0	1
Head injury	2	0	0	0	2
Other (timing uncertain):					
Height on or below 3rd centile	30	10	8	3	9
Head circumference on or above 97th centile	10	4	3	2	1
Epilepsy	9	0	5	2	2
Behaviour problems	21	2	13	2	4
Three or more minor malformations	10	2	3	2	3
Incoordination	42	4	27	4	7

children with IQs of more than 70, eight (11%) had behaviour problems, compared with 11 (12%) of those with IQs of less than 70 (two children were not tested).

Ten survey children (6%) had three or more dysmorphic features unrelated to chromosome abnormalities or recognised syndromes. In the control group the corresponding frequency was two of 55 (4%).

Forty two children (25%) had incoordination, four of whom had no other risk factors identified. Twenty seven had known risk factors: chromosome abnormality ($n=5$), a recognised syndrome ($n=2$), microcephaly ($n=3$), congenital adrenal hyperplasia ($n=1$), perinatal stress ($n=13$), meningitis ($n=1$), head injury ($n=1$), and status epilepticus ($n=1$). Incoordination was not a feature in the two boys with XXY, the girl with the X-autosome translocation, and two of the three children who had infections of the central nervous system. Four of the control children (7%) had incoordination.

Parental education

Parental educational problems were defined as attendance by the parent at a school for the mildly mentally retarded, or an admission of illiteracy or semiliteracy. For a child to be designated as having parents with educational problems, such a history was required from both parents. There was a history of educational problems in the parents of 86 children. Table 4 shows the incidence of parental education problems in children with known risk factors, those with a single possible risk factor, those with two or more possible risk factors, and those in whom no medical features were identified. The percentage of parents with educational problems was lowest in the first of these groups (39%), and highest in the last (77%). Eight children with

parents of average or superior education had no medical features identified in their history or examination, and a further 17 had just one possible risk factor.

Discussion

The attribution of mild mental retardation to medical factors is fraught with difficulties. There is no good working definition of the phenotype, many of the relevant medical factors are open to subjective interpretation, and control data are inadequate, especially in the rapidly changing specialty of perinatal care. Despite these difficulties it is an area requiring medical study. Parents generally appreciate a medical 'label', and genetic counselling may be important. Recent study of the fragile X syndrome^{7,8} has shown that medical factors are not confined to severely retarded children. It has often been assumed that most mild retardation is multifactorial. If the distribution of IQs was normal, 3% of the population could be expected to have IQs of less than 70. We found that 2% of the Southampton schoolchildren aged 7-11 were attending schools for the mildly mentally retarded at the time of our survey, but only half of these were in the IQ range 50-70. The factors apart from IQ that influence referral for this type of special education are not clear. Parental approval is required, and referral must be to some extent dependent on facilities for remedial education available in normal schools. We expected (but did not find) that children with IQs of over 70 would be more likely to have behaviour problems. Selection could bias the study sample either towards or away from identifiable medical causes.

Over a quarter of the children in the schools for the mildly mentally retarded were not included in the survey. Parents of 31 children actively declined to take part and although no reason for refusal was sought two explained that this was because their children had already been thoroughly investigated, and a further nine stated that they did not wish to submit their children or themselves to venepuncture. Nineteen families did not respond and were not available for two home visits at prearranged times. Sociocultural problems may be important in these families, and their exclusion could have biased the population sample.

The risk factors shown in table 1 are plausible explanations of mental retardation, although some doubt must remain about the individual importance of the perinatal features. Comparison with paired sibling controls showed a significant excess of perinatal problems in the index patients. Some of these are, however, subjective or poorly standar-

Table 4 Medical features and parental education of 169 mildly mentally retarded children

	No of children	No (%) of children of whom both parents had educational problems
Features of known aetiological importance (with or without other possible risk factors)	71	28 (39)
Two or more possible risk factors	26	11 (42)
One possible risk factor	37	20 (54)
No medical features	35	27 (77)
Total	169	86 (51)

dised, and there is always the possibility that perinatal difficulties are secondary. Other factors, including the child's original potential, may reduce or enhance the consequences of early brain damage. Bearing in mind these caveats, perinatal events of the type we have reported must be considered as having potential aetiological significance.^{9 10}

Medical factors having a probable association with mild mental retardation were identified in 71 of these children (42%). Hagberg¹ in a study of 91 Swedish children with IQs of 50–70, found similar factors in 43%. From the results of our survey we believe that reduction of the genetic contribution to mild mental retardation by appropriate genetic counselling would not be feasible. The eight chromosomal abnormalities had all arisen *de novo*, though four of the mothers were over 35 years when the children were born. All children in the survey were born before August 1976. More recently their mothers might have been offered amniocentesis. Three other children had prenatal genetic defects (Sotos' syndrome, Aarskog's syndrome, and congenital adrenal hypoplasia), but in all three the genetic defects became apparent only after the birth of the children. Alcohol fetopathy was found in only one child in contrast with the Swedish study¹ in which 8% of mildly retarded children had the fetal alcohol syndrome.

We have not so far been able to account for the lack of fragile (X) chromosome cases in our sample. Extrapolating from the data of Webb *et al*⁷ we should have expected five affected boys in our age group in Southampton, two or three of whom might have been at schools for the mildly mentally retarded, plus perhaps four or five affected girls. The relevant cytogenetic techniques leave scope for variability, but the laboratory did make this diagnosis on samples from other sources during the period of the survey.

Though no firm conclusions could be drawn from the group of 63 children who had possible risk factors alone, certain points emerged. Maternal diabetes was the sole medical feature in three children. Children born to diabetic mothers are at increased risk of physical abnormalities¹¹ but we are not aware of any previous association with mental retardation. One of these children, who had parents of normal intelligence, had a brother who was also retarded. Thirty children (18%) were of small stature. In two, this could be related to medical conditions (fetal alcohol syndrome and severe per-tussis), but in 28 children there was no obvious cause. In 10 children small stature was the only medical feature noted. The association between small stature and mild mental retardation is not clear, but there may be an interaction between the

behavioural attributes of the parents and the child.¹² Incoordination, which featured in 42 children (25%) was associated with known risk factors in 27 (13 with perinatal stress). In contrast, Hagberg¹ found that 43% of mildly retarded children had a neurological abnormality, but does not give details of the method of assessment used.

Children in all the aetiological groups had parents who had had educational problems, but the proportion was highest (77%) in 27 children with no recognised medical risk factors; in 37 children with just one possible risk factor, parents of 20 had had educational problems. Polygenic factors may contribute appreciably to the mental retardation in these two groups of children, but similar findings could be produced by as yet undetected major familial factors such as single gene defects.

We found no previously unrecognised errors of metabolism in the mothers or children in the survey, hence routine biochemical testing would not seem appropriate in the aetiological investigation of children at these special schools. We recommend careful physical examination of the children by school medical officers, looking especially for minor dysmorphic features. Referral to a paediatrician or geneticist should be considered if three or more dysmorphic features are found, or if a genetic syndrome is suspected. We recommend chromosome analysis for all mildly mentally retarded children irrespective of whether there are any dysmorphic features. Finally, in assessing the children account should be taken of the level of parental intelligence and of any possible contributory features in their history, but in some children no cause for the retardation will be found. There were eight children in this survey who had parents of normal intelligence and no medical features identified, and a further 17 (again with normal parents) who had just one feature of uncertain relevance to account for their retardation. It was beyond the scope of this study to investigate these children further, but identification of children with idiopathic mild mental retardation and their further neurological investigation might be of value.

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The socio-familial background and prevalence of medical aetiological factors in children attending ESN/M schools

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ABSTRACT. A study of 169 mildly mentally retarded children included consideration of social class, medical risk factors, sibship position, family size and parental education. Ninety-four (56%) children were from social class IV or V. Medical risk factors were identified in 71 (42%) children overall: the prevalence fell from 55% in social class II to 30% in social class V. Prenatal factors were identified in 22 children of whom 14 were third or later born in their sibship: this may reflect increased maternal age at birth. Perinatal events had been reported in 41 children, 20 of whom were in social class III; there was no clear relationship to sibship position. Seven of eight postnatal events had occurred in children in social class II or III. Children in social class IV or V did not appear to be at increased risk of retardation from environmental medical events. First-born children were over-represented in the survey, with a minor shift towards fourth- or later-born children. Average family size was 3.25 children (general population 2.0 children). The prevalence of medical risk factors was lowest (18%) in children from large sibships in social class V. Both parents of 86 children had had educational problems: this included 13 children in social class III. Thirty-eight (33%) of these children had medical risk factors, compared with 43/83 (51%) in children where at least one parent had achieved average education. Thirty children had no medical risk factor, nor any history of parental learning difficulty.

INTRODUCTION

An association between mild mental retardation and social class was identified by Penrose in 1938, in a study of 1280 retarded individuals. Whereas severe mental retardation was evenly distributed in all social groups, patients with mild mental retardation came predominantly from the lower social classes. He also noted that mental subnormality was more in evidence in parents of high-grade defectives than in parents of imbeciles or idiots. Penrose carried out his survey on patients in an institution, but community surveys (Drillien *et al.*, 1966; Birch *et al.*, 1970; Morton *et al.*, 1977) have since confirmed his observations.

Medical pathology—genetic, environmental or both—of aetiological relevance is identified more frequently in severe than in mild retardation (Hagberg *et al.*, 1981; Einfeld, 1984), but for any given insult the final outcome in level of intellect will depend on a child's initial potential and subsequent socio-cultural influences. A child's motivation for learning will be influenced by the intellectual and emotional support provided at home. Hence, in a study of children with mild mental

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Average: literate, no history of educational problems at school, regular school attendance, possibly—but not necessarily—leaving school with a formal certificate of education;

Low: semi-literate, attendance at normal school but requiring special help;

Very low: illiterate, attendance at ESN/M school.

Medical Assessment

Medical factors identified in the children were grouped into those associated with risk of mental retardation (group A) and those in which any link with retardation is more tenuous (group B). Consideration of medical factors in this paper is limited to those in group A and, within this group, to primary medical features (for example, a child with hydrocephalus and neonatal twitching is listed solely under pre-natal causes). The full range of medical features and their inter-relation from the subject of another paper (Lamont & Dennis, 1988).

Medical features involving risk of mental retardation were grouped as pre-, peri- or post-natal.

Pre-natal factors: chromosomal aneuploidy or imbalance
 recognized genetic syndrome
 CNS malformation
 metabolic defects
 intra-uterine infection
 foetal alcohol syndrome

Peri-natal factors: foetal distress
 apgar score ≤ 6 at 5 min
 neonatal twitching or cyanosis

Post-natal factors: CNS infection
 intracranial haemorrhage
 prolonged apnoea

The pre-natal factors noted all have a recognized association with mental retardation. Malformations without evident CNS involvement, for example, cleft palate and limb abnormalities, were not included.

Peri-natal factors were limited to recorded signs of adverse effects on the foetus or neonate. Antepartum haemorrhage, instrumental delivery or admission to the special care nursery were not included if there was no evidence of anoxia or cerebral irritation.

Post-natal factors were included only where they led to developmental delay not previously present.

RESULTS

The social class of children in the survey and the distribution expected from census figures for an equal number of children in the general population are shown in Fig. 1.

There were no children in social class I and IX (expected number 41) in social

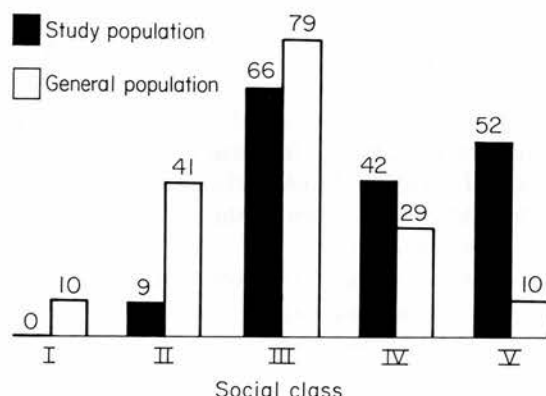


Fig. 1 Social class distribution of children attending ESN/M schools and in the general population ($n=169$).

class II. In social classes IV and V, there was an excess of study children, 94 (56%) as against 39 (23%) expected. This was a highly significant shift in distribution ($P<0.001$).

The prevalence of identified medical risk factors pre-, peri- or post-natal in each social class is shown in Table 2. The overall prevalence of medical features fell from 55% in class II to 30% in class V ($0.05<P<0.02$). Pre-natal factors were identified in 22 (13%) children. No children in social class II had pre-natal features; in social class III, IV and V the prevalence was 15%, 19% and 7.6% respectively. Peri-natal problems were the most frequent medical association in the study group: overall they occurred in 41/169 (24%) children. They had been recorded in 20/66 (30%) children in social class III. In social class IV and V, the incidence was 19% and 23%, respectively. A post-natal medical event which could have resulted in mental impairment had occurred in four of the nine children in social class II, but in only one of 94 children in social classes IV and V.

Table 2 Social class and medical risk factors in 169 ESN/M children

Social class	<i>n</i>	Pre-natal	Peri-natal	Post-natal	Total (%)
II	9	0	1	4	5 (55)
III	66	10	20	3	33 (50)
IV	42	8	8	1	17 (40)
V	52	4	12	0	16 (30)
Total	169	22	41	8	71 (42)

Family size

The average family size of the study population was 3.25 children. In the general population at the 1981 census, average family size was 2.00 children.

Table 7 Medical risk factors sibship position in 169 ESN/M children

	Sibship position			
	One	Two	Three	≥Four
Number	57	57	26	29
Medical features (per cent in group)	25 (44)	18 (32)	13 (50)	15 (52)
Pre-natal	5 (9)	3 (5)	6 (23)	8 (28)
Peri-natal	17 (30)	12 (22)	5 (19)	7 (24)
Post-natal	3 (5)	3 (5)	2 (8)	0 (0)
No medical feature	32 (56)	39 (68)	13 (50)	14 (48)

Parental education

Using the standards already described, both parents of 115 children were assessed as having a level of education within the same 'grade': superior, average, low or very low (Table 8). In the remaining families, the level of parents' education fell within adjacent grades. In 37 families, where the natural fathers were not interviewed reliance had to be placed on what the mothers said. In 62 families, both parents had achieved an average or superior standard of education. In seven families, one or both parents had received formal education over the age of 18 years; these, and two families where both parents were of average educational attainment, were in social class II. In 21 families—10 from social class III—one parent was of average, and one of low educational attainment.

Educational problems had occurred in the mother in 11 of these families. Of 86 families where both parents had low educational achievement, 13 were in social class III: of 18 families where both parents were illiterate, or ESN/M, three were in social class III, with fathers who, after ESN/M education, became drivers of heavy goods vehicles.

Of 83 children where at least one parent was of average educational attainment medical factors were identified in 43 (51%). Where both parents had had learning difficulties, 28/86 (33%) children had medical risk factors ($0.02 > P > 0.01$).

Table 8 Parental education, social class and medical risk factors in 169 ESN/M children

Parental educational grading (see text)	Social class				Total	Medical features
	II	III	IV	V		
Superior/superior	3	—	—	—	3	1
Superior/average	4	—	—	—	4	1
Average/average	2	43	10	0	55	30
Average/low	—	10	9	2	21	11
Low/low	—	7	11	21	39	10
Low/very low	—	3	11	15	29	12
Very low/very low	—	3	1	14	18	6
	9	66	42	52	169	71

There were 30 study children with no medical risk factors, nor any history or parental educational problems.

DISCUSSION

This study did not include 50 children who would have been eligible had their parents agreed to take part. Thirty-one parents refused to participate. For the 22 who said 'no' by post, reasons are not known, but the request for a blood sample from mother and child was the apparent reason for refusal in the nine families who were seen at home and did not wish to enter the study. An aversion to venupuncture is unlikely to be associated with the factors under consideration in the study, and non-inclusion of this group should not bias results unduly. There were also 19 families from whom no response was obtained, either to the original letter or to two home visits arranged by letter. The authors recognize that omitting this group may have biased the study in favour of parents who were cooperative and perhaps also of those who were literate.

For children in the study, social class distribution and family size were quantitatively assessed, and related to those in the general population: the sibship position was related to that expected statistically. Such comparisons do not indicate specific aetiological factors but may indicate, if only indirectly, social factors possibly contributing to mild mental retardation. Social conditions may have a secondary association with mental retardation if they have an association with medical risk factors.

There were no study children in social class I. This may reflect use of private education by parents in this group and such parents might have an increased preference for private education for a child who appeared to be of below average intelligence. This factor may be operating to a lesser extent, in social class II: there were nine children in this group, considerably lower than the 41 equivalent in the general population. It is not likely to have any significant effect on distribution in social classes III, IV and V. Sixty-six (39%) children in the survey came from social class III; 94 (56%) from social classes IV and V, as compared to 23% in the general population. With the known association of mild mental retardation and lower social class, the shift in social class distribution was not unexpected. It was slightly surprising, however, to find in this study that just 56% of children came from social classes IV and V. In recent studies, 78% of children with mild mental handicap in Mannheim were from the lower social classes (Cooper & Lackus, 1984); in Montreal (Larson & Lapointe, 1986), 94% of 77 adolescents with mild to moderate mental handicap were from social class IV or V. The low educational attainment of parents of 23 of the 66 children from social class III may have contributed to the need of ESN/M education by their children. Family size was significantly increased in the study children, with the prevalence of sibships \geq four in social class V double that in social class III. Large families may tend to occur more frequently in lower social class (Kushlick & Blunden, 1974) but, even so, they were over-represented in this survey. Children from large sibships have been shown to have lower intelligence ratings than those from sibships of \geq three (Anastasi, 1956) and, hence, will be more prone to overt

learning difficulty; any adverse influence on brain development may enhance this trend. There was no suggestion from the study that first-born children are at increased risk of mental retardation. On the contrary, with 57 first-born as opposed to 67.5 expected, the 'first-born' phenomenon (Clarke & Clarke, 1974)—whereby first-born children tend to be superior to their siblings—may be pertinent. The shift in sibship position towards fourth- or later-born children suggested that, in large sibships, younger children may be at increased risk of retardation possibly reflecting risk factors associated with increased maternal age.

Medical factors which could contribute to mental retardation were identified in 42% of the children. The pre-natal features included were evident from clinical examination or laboratory analysis and have a definite link with mental retardation. Peri-natal features, which accounted for 41/71 medical risk factors identified, had to be based on retrospective data. Apgar scores of children born in peripheral hospitals were not routinely recorded and foetal distress was diagnosed by use of the foetal stethoscope. The long-term effect of peri-natal stress on intellectual capacity has been the subject of much debate and is still questionable. Nevertheless, the author felt that a history of foetal distress, low apgar score, or neonatal cyanosis or twitching constituted a medical risk factor in these mildly retarded children. Post-natal events, also based largely on retrospective data, were included only where developmental delay occurred subsequently.

The prevalence of medical risk factors fell gradually from 55% in children in social class II to 30% in social class V; it was lowest (18%) in children from large families in social class V. This was the group of children most likely to be exposed to a poor socio-cultural environment. The overall performance did not vary greatly with sibship position.

Pre-natal features such as chromosome abnormalities or sporadic syndromes associated with mental retardation will occur independently of social class, and were found in children from social classes III, IV and V. None were found in children from social class II but numbers here (nine) were low. Environmental pre-natal factors of pathological significance had occurred in just three children with no social class bias. The prevalence of pre-natal factors was highest in third- and later-born children: a possible association with maternal age has already been mentioned.

Peri-natal problems had occurred most frequently in women in social class III with no indication that children born to mothers living in poor social conditions were at possible increased risk of retardation from obstetric problems. They would be expected to occur more often in *primi-parae* and *grand multiparae*. Seventeen of 57 (30%) first-born children had had recorded peri-natal distress, as had 7/29 (24%) fourth- or later-born children; but 22% of second-born children, and 19% of third-born children, had also had birth problems; there was no clear association with sibship position.

Post-natal problems had occurred in just eight children: too few for statistical analysis. It was of interest to note, however, that none of these eight children came from social class IV or V. One child, with a non-accidental head injury which left her with a left hemiparesis, came from social class II. Three children who had had infections of the central nervous system all had good home conditions. Babies in poor

social conditions are recognized as being at increased risk of cot death (Golding *et al.*, 1985) but two study children found cold, limp and apnoeic in early life, who could be regarded as 'rescued cot deaths' were not in this high-risk category. Post-natal problems were confined to first-, second- and third-born children. The few cases of post-natal problems did not provide any evidence that younger children in large families are at any increased risk of mental retardation arising from injury or CNS infection.

In both parents of 86 children, educational attainment was limited to low or very low levels and in a further 21 children one parent had a low educational level; these families were not confined to social classes IV and V. Such children may have limited initial potential and receive little, if any, intellectual support at home. Such a combination may have been the main factor leading to referral to ESN/M schooling in 68 children but 39 (36%) had, in addition, medical features which could also have contributed. Sixty-two children where both parents had achieved average education or above had a higher prevalence of medical factors (52%), but it was of interest to note that 30 children in this group had no medical risk factors identified.

Overall, results from this survey suggest that while proportionally more children from social classes IV and V receive special education in ESN/M schools, the presence of parental learning difficulty is an influential factor behind referral. Medical risk factors featured in all groups of children in the survey, but there was a group of 30 children whose parents had had no educational problems and in whom no medical risk factors were identified.

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